EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/641081/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyvgart

International non-proprietary name: efgartigimod alfa

Procedure No. EMEA/H/C/005849/0000

Note

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

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List of abbreviations

Ab	antibody
AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	anti-acetylcholine receptor antibody
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AUC	area under the concentration-time curve
BLA	Biologics License Application
C1	first treatment cycle
C1B	baseline of cycle 1 (also study entry baseline [SEB])
CL	clearance
Cmax	maximum observed concentration
CMC	chemistry, manufacturing, and controls
CMI	clinically meaningful improvement
Cn	treatment cycle, n (number)
CnB	baseline of cycle, n (number)
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	trough concentration (measured concentration at the end of a dosing interval)
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EFG	efgartigimod
EMA	European Medicines Agency
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration (also referred to as "the Agency")
gMG	generalized myasthenia gravis
GCP	Good Clinical Practice
Ig	immunoglobulin
IA	interim analysis
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRR	infusion-related reaction
ISE	Integrated Summary of Efficacy
ITC	intertreatment cycle
ITP	immune thrombocytopenia
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
LRP4	low-density lipoprotein receptor-related protein 4
mAb	monoclonal antibody
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 Myasthenia Gravis Quality of Life scale (revised version)
MMF	mycophenolate mofetil
MSE	minimal symptom expression
MuSK	muscle-specific kinase
MW	molecular weight
NMJ	neuromuscular junction
NSID	nonsteroidal immunosuppressive drug
OR	odds ratio
PB	pooling block (number)
PBO	placebo
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

PLEX	plasmapheresis/plasma exchange
q4d	every 4 days
q7d	every 7 days
QMG	Quantitative Myasthenia Gravis
QoL	quality of life
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEB	study entry baseline
SOC	system organ class
t½	half-life
TC	treatment cycle
TEAE	treatment-emergent adverse event
TP	treatment period
URTI	upper respiratory tract infection
UTI	urinary tract infection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Argenx submitted on 30 July 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Vyvgart, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

Vyvgart was designated as an orphan medicinal product, orphan designation number EU/3/18/1992 on 21/03/2018 in the following condition: treatment of generalized Myasthenia Gravis (gMG).

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

The applicant applied for the following indication: "the treatment of generalized Myasthenia Gravis".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP). An initial PIP was approved on 18 March 2020 (Decision number P/0097/2020) and was subsequently modified (17 March 2021 – Decision number P/0072/2021).

At the time of submission of the application, the PIP P/0072/2021 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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance efgartigimod alfa contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant did not seek protocol assistance from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Dr Alexandre Moreau

The application was received by the EMA on	30 July 2021
The procedure started on	19 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 February 2022
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	29 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 April 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2022
The outstanding issues were addressed by the applicant during a clarification meeting before the CHMP during the meeting on	02 May 2022

The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 June 2022
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	23 June 2022
The CHMP adopted a report on similarity of Vyvgart with Soliris on (see Appendix on similarity)	23 June 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 June 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initial claimed indication for efgartigimod alfa was "the treatment of generalized Myasthenia Gravis".

Generalized myasthenia gravis (gMG) 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 (NMJ), which causes debilitating and potentially life-threatening muscle weakness.

2.1.2. Epidemiology

In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 myasthenia gravis (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 (generalised MG). 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.

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 (eg, 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 NMJ, leading to failure of neuromuscular transmission. Anti AChR autoantibodies are of the IgG1 and IgG3 subtypes. Anti-MuSK autoantibodies are IgG4 subtype and do not activate the complement pathway.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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 (QoL).

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 or rituximab are used for more refractory cases (Table 1).

Table 1 – Therapies currently used for Myasthenia Gravis

Therapy	Mechanism of Action	Side Effects/Limitations	Approval Status in EU
AChE inhibitors	Acetylcholine breakdown inhibition, increasing its availability in the NMJ	Short-acting and often needs to be taken several times daily[6,11]	Approved for the treatment of MG
Corticosteroids More commonly used: oral prednisone	Nonspecific immunosuppression	Widespread short- and long-term adverse effects[29,35,41,42]	Not approved for the treatment of MG in all EU member states
NSIDs More commonly used: Azathioprine, cyclosporine, and mycophenolate Also used: tacrolimus, methotrexate, and cyclophosphamide	Multiple mechanisms of action, including suppression of B and T cells	Various side effects, including liver and bone marrow toxicities, malignancies, and increased risk of infection for the more commonly used NSIDs[27,43,44]	With the exception of recently approved azathioprine (Jayempi®), not approved for the treatment of MG in all EU member states
Intravenous immunoglobulins	Multiple mechanisms postulated including effects on autoantibodies, B and T cells	-IVIg use is limited in patients who are at risk of renal dysfunction and have a history of hypertension or risk factors for thrombotic events[48] -Burdensome administration -Supply chain shortages are common -Nausea, headache, fever, hypotension or hypertension, local skin reactions, IgA deficiency, allergic reactions	With the exception of Gamunex 10% solution for infusion, not approved for the treatment of MG
Plasma exchange	Removal of autoantibodies and complement components	-Invasive procedure -Hospitalization required -Use limited by requirements for specialist administration and venous access issues[43,46,47]	Not approved for the treatment of MG
Rituximab	B-cell depletion	-Nausea, infections, infusion-related problems -Progressive multifocal leukoencephalopathy	Not approved for the treatment of MG
Eculizumab	Complement inhibitor, prevents C5 cleavage and inhibits IgG autoantibody-initiated complement activation	-Limited to treatment of refractory MG[32] -Increased risk of *Neisseria meningitidis* infection and the need for vaccination prior to commencing treatment[37]	Approved for the treatment of AChR-Ab positive patients with refractory gMG

AChE=acetylcholinesterase; AChR-Ab=anti-acetylcholine receptor antibody; C5=complement component 5; EU = European Union; gMG=generalized myasthenia gravis; IgA=immunoglobulin A; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; MG=myasthenia gravis; NMJ=neuromuscular junction; NSID=nonsteroidal immunosuppressive drug

Plasmapheresis/plasma exchange (PLEX) and intravenous immunoglobulins (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, the complement inhibitor eculizumab, and azathioprine, which have received regulatory approval in Europe for the treatment of gMG, 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 maintain disease control in prospective double-blinded studies (Tindall 1993[6], Yosikawa 2011[7]). In a phase 3 study, mycophenolate mofetil (MMF) 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 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 Summary of Product Characteristics 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

[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
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[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 managementof myasthenia gravis: executive summary. Neurology 2016;87:419–425

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.

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 eculizumab is approved only for AChR-Ab seropositive patients and is limited to treatment of refractory MG.

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 plasma exchange (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.

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 neonatal Fc Receptor (FcRn). Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies.

Pharmacological classification: L04AA58, immunosuppressants, selective immunosuppressants.

The initially claimed indication for efgartigimod was *"Vyvgart is indicated in adults for the treatment of generalised Myasthenia Gravis (gMG)".*

The final approved indication is: "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 recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was

not considered to be of major public health interest. This was based on the uncertainty related to the intended broad indication (and thereby questioning of whether the product does in fact fulfil an unmet medical need) as well as the potential long-term safety issues deriving from the reduction of IgG levels.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion (sterile concentrate) containing 400 mg (20 mg/mL) of efgartigimod alfa as active substance.

Other ingredients are: sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, sodium chloride, arginine hydrochloride, polysorbate 80 and water for injections.

The finished product is available in single-dose 20 mL glass vials (type I) with rubber stopper (butyl, siliconised), aluminium seal and polypropylene flip-off cap.

2.4.2. Active substance

General information

Efgartigimod alfa is a human immunoglobulin (Ig) G1 (hIgG1)-derived Fc fragment of the za allotype targeting the neonatal Fc receptor (FcRn). The efgartigimod alfa Fc fragment is a homodimer consisting of two identical peptide chains of 227 amino acids each.

Efgartigimod alfa contains a N-glycosylation site at position Asn with the predominant glycan being of the G0F format. The C-terminal lysine is predominantly clipped. Abdeg ("antibodies that enhance IgG degradation") mutations have been introduced in the efgartigimod alfa molecule in order to increase its affinity for FcRn also at neutral pH. As a result, efgartigimod alfa binds to FcRn with a higher affinity (nanomolar) than wild-type IgGs, up to neutral pH. The general properties of efgartigimod alfa active substance have been adequately provided in the dossier.

Manufacture, process controls and characterisation

The sites employed in the manufacture of the active substance is Lonza Biologics Slough, UK and Lonza Biologics Tuas, Singapore.

The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with good manufacturing practice (GMP).

Description of manufacturing process and process controls

The manufacturing process for efgartigimod alfa active substance is based on a recombinant Chinese hamster ovary (CHO) cell line, containing the DNA sequence for the efgartigimod alfa protein. The process is based on the applicant's platform knowledge of standard monoclonal antibody manufacturing. In brief, a cell culture upstream process consisting of the following steps: thaw of one working cell bank (WCB) vial, expansion of cells, inoculation of the production bioreactor, harvest, clarification, filtration, followed by downstream purification including chromatography steps, specific virus

inactivation/reduction steps, concentration, diafiltration into the formulation buffer, sterile filtration and dispensing into active substance storage containers.

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

Possibility of reprocessing is suggested for some processes steps. Sufficient validation data has been presented supporting the proposed possibilities for reprocessing.

The batch scale is defined by the size of the production bioreactors at site Lonza, Slough, UK or Lonza Biologics Tuas, Singapore. Apart from facility specific adaptations, the process conducted at Slough and Tuas is identical and has been demonstrated to produce material of comparable quality by comprehensive comparability studies.

The estimated number of reuse cycles for each of the chromatographic columns, at both manufacturing sites Slough and Tuas, were provided. The justification is found acceptable.

Overall, the efgartigimod alfa active substance manufacturing process has been adequately described. The active substance manufacturing process is considered acceptable.

The container closure system for efgartigimod alfa active substance is a sterile high-density polyethylene (HDPE) container with a polypropylene (PP)closure. Compliance of all container closure system materials with relevant Ph. Eur. monographs has been confirmed by the applicant. No incompatibilities between the active substance and container components of the bottles or bags have been observed. The active substance container closure systems are found acceptable.

The risk analysis regarding potential extractables and leachables has been presented for each manufacturing site. It was concluded that the risk is negligible and no items were identified as potentially impacting the safety or quality of the active substance. This conclusion is endorsed.

Control of materials

Raw materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. 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 alfa active substance, except for the recombinant CHO production cell line. The system in place is considered appropriate for ensuring the quality of the raw materials used for the manufacture of efgartigimod alfa active substance.

Source, history, and generation of the cell substrate has been adequately presented in the dossier.

Cell banking

A two-tiered cell banking system is used and sufficient information is provided regarding testing of master cell bank (MCB) and WCB and release of future WCBs. One vial of the research cell bank (RCB)was used to generate MCB, from which a WCB was generated. The cell banks have been qualified in accordance with ICH Q5A and ICH Q5D. The results of the cell bank characterisation studies were as expected. No adventitious agents were detected and no endogenous retrovirus was detected, except for the expected presence of retrovirus like particles (RVLP). The MCB and WCB are overall considered appropriate starting materials for the manufacture of efgartigimod alfa active substance. The genetic stability of cell banks and the production cell line was confirmed. Cell bank characterisation for MCB and WCB is considered sufficient to ensure consistency. A protocol for generation and characterisation of

future working cell banks has been provided. The protocol is in line with current guidance and considered acceptable.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls (IPCs) and critical in-process tests performed throughout the efgartigimod alfa active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Critical process parameters (CPPs) have been identified. In addition to IPCs for bioburden and endotoxin, the microbial quality of efgartigimod alfa active substance is ensured through manufacturing process design for minimisation of risk of introduction and proliferation of microbial contaminants and through implementation of validated in-process hold times.

Process validation

The efgartigimod alfa commercial manufacturing process was developed and validated at commercial scale at Lonza Biologics, Slough, UK by the manufacture of process performance qualification (PPQ) batches. CPPs and selected non-CPPs were monitored during the PPQ campaign to demonstrate that the active substance 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. Acceptance criteria for process validation parameters were established.

The initial cell culture, harvest and downstream process validation was executed. The validation encompassed process performance qualification batches derived from the same working cell bank and demonstrated acceptable process performance and batch to batch consistency. The purification process demonstrated consistent and effective removal of process-related impurities. All PPQ batches complied with the applied release acceptance criteria. In-process control and release test results from the PPQ batches were all compliant with the acceptance criteria and no atypical results were observed. Following process validation at Lonza Biologics, Slough, UK the efgartigimod alfa process was transferred to the additional active substance manufacturing site, Lonza Biologics, Tuas, Singapore. The process was validated by PPQ studies of PPQ batches, applying the overall same validation strategy as for the process at Slough. Results obtained during process validation provide documented evidence that the cell culture, harvest and purification process is validated and consistently produces efgartigimod alfa active substance that meets pre-defined acceptance criteria. In addition, the bulk active substance for all PPQ batches met final release specifications.

In conclusion, both commercial scale manufacturing process conducted at Lonza Biologics Slough and Tuas, respectively, has been successfully validated through the PPQ studies performed at the respective sites. A continued process verification (CPV) program was implemented at both manufacturing sites following process performance qualification in order to demonstrate an ongoing state of control over the lifecycle of the product.

In addition to the PPQ campaigns at Slough and Tuas sites, supporting process validation studies were conducted to support the finished product process validation.

Manufacturing process development

The efgartigimod alfa active substance manufacturing process has been developed by Lonza. Three major process versions have been used to manufacture efgartigimod alfa active substance: Process 0, (used for non-clinical safety studies and initial Phase 1 and Phase 2 clinical trials), Process 1 at Lonza Biologics, Slough, UK, (used for non-clinical safety studies, Phase 1, Phase 3 clinical trials and commercial

manufacturing) and Process 2 at Lonza Biologics, Tuas, Singapore (for commercial manufacturing). The changes implemented have been adequately described and justified.

Comparability studies were conducted in accordance with ICH Q5E. For the comparability assessment, results generated using the release test methods were evaluated against the release test acceptance criteria applicable at the time of testing and extended characterisation results, including forced degradation studies, were evaluated based on method performance and product knowledge. Side-by-side analytical testing was conducted in order to minimize impact from assay variability where relevant. A total of four comparability studies have been conducted. In addition, comparison of finished product batches derived from the active substance material of the process versions in question was conducted. Comparability was demonstrated throughout the active substance process development. Furthermore, all four comparability studies demonstrated that the finished product manufacturing process does not affect the quality attributes determined at active substance level, irrespective of the active substance manufacturing process used. Therefore, comparability at active substance level can be extended to cover finished product level as well.

Characterisation

The characterisation studies are considered comprehensive and adequately covering the relevant structural (primary and higher order), physicochemical and biological attributes of efgartigimod alfa as well as the impurities potentially present. The following quality attributes were analysed: molecular weight, amino acid sequence, disulfide bonding, secondary and tertiary structures, glycosylation profile, biological activity, size-related and charge-related variants and other product-related substances and impurities.

Intact N-terminus was present, while low levels of N-terminal truncated variants were observed. Isomerisation of aspartic acid was observed. Deamidation was observed at the three sites. With regards to oxidation, one methionine site is observed to be oxidated at low levels. Based on extensive characterisation, it is concluded that the impact on potency from the methionine oxidised variant is small.

The glycosylation site was identified and glycans have been thoroughly analysed. The N-linked glycans were predominantly neutral, with low levels of charged glycans. The observed major glycoforms are naturally occurring in humans and are therefore expected to present minimal immunogenicity or safety risk.

Size-related variants were characterised by the use of gel permeation high performance liquid chromatography (GP-HPLC) and SEC-MALS, for high molecular weight (HMW) species/aggregates, and capillary electrophoresis sodium dodecyl sulphate (CE-SDS), for low molecular weight (LMW) species (fragments). Efgartigimod alfa aggregates may lead to increase immunogenicity and may further have an increased affinity to FcRn. Aggregates could thus trigger FcRn clustering which could lead to increased side-effects and lead to a shorter PK profile resulting in a reduced efficacy. Appropriate control strategy has been described by the applicant to limit the formation of HMW and LMW species.

Charge-related variants have been characterised by imaged capillary isoelectric focusing (icIEF). The identity of the icIEF isomers was further characterised by fractionation on anion exchange chromatography and RPLC-MS.

The process related impurities have been adequately identified and related control strategy appropriately defined. The results of the characterisation studies performed showed that efgartigimod alfa active substance has the expected structure of an IgG1 Fc fragment with increased binding specificity for FcRn in comparison with wild-type IgGs. Furthermore, heterogeneity of the active substance was adequately characterised. In summary, the characterisation is considered appropriate for this type of molecule.

Specification

The active substance specification complies with the provisions of ICH Q6B and includes: testing for visual appearance, content, identity, purity, potency, polysorbate (PS) 80 concentration and impurities. Furthermore, required testing for absence of mycoplasma and adventitious viruses is performed as in-process controls on unprocessed bulk harvest, which is deemed acceptable.

According to the applicant, the following factors were evaluated in relation to determination of acceptance criteria for the critical quality attributes monitored at release: regulatory requirements and compendial standards, preclinical and clinical exposure, process capability, size of analytical data set used, method variability, stability data and formulation robustness study data, where relevant, in addition to standard statistical analysis evaluating range, average and tolerance interval (95% confidence). Stability data were excluded from the statistical analysis for stability-indicating analytical methods. Data used for defining acceptance criteria derive from batches representing all process versions used at Lonza. Overall, the acceptance criteria defined are considered well justified and acceptable. During the assessment, the tightening of some acceptance criteria has been requested and implemented by the applicant.

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

Analytical methods

The applicant has provided brief, but adequate descriptions 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 have been verified for suitability for testing of the efgartigimod alfa active substance. Non-compendial analytical methods (identity, purity, potency, protein concentration and determination of PS80 concentration) have all been validated according to ICH Q2. Validation reports have been provided. The documentation provided for the validation of analytical procedures for efgartigimod alfa active substance is considered comprehensive.

The assay used for determination of potency of the efgartigimod alfa active substance has been adequately determined.

Batch analysis

For the process at site Slough, batch data have been provided. The PPQ batches have all been placed on stability. Furthermore, release data have been provided from batches, manufactured from 2014 to 2019. These include batches used for non-clinical and clinical studies and batches used for establishment of reference standards.

For the process at site Tuas, batch data have been provided from the PPQ batches manufactured at the Tuas site, using process intended for commercial purposes. The PPQ1-3 batches have been placed on stability. Furthermore, release data have been provided from two batches used for clinical purposes and stability.

The batch analysis data provided cover batches from all process versions throughout development. All results comply with the specification in place at the time of testing and batch-to-batch consistency is demonstrated. Comparability of batches manufactured using different process versions has been demonstrated by extensive comparability studies.

Reference materials

The quality of efgartigimod alfa active substance and finished product is monitored by a two-tiered reference standard approach with a primary reference standard (PRS) and a working reference standard

(WRS).The current primary reference standard and the current working reference standard are both derived from the same clinical phase 3 batch. Comparability has been demonstrated throughout development and active substance material from a former process is representative of the material from the commercial process. The qualification of PRS and WRS included testing according to the active substance release test specification and comprehensive extended characterisation, and comparison with the previous reference standard.

All batch release data complied with the acceptance criteria in place at the time of testing. From the extended characterisation data, comparability was demonstrated between the previous primary reference standard. As the PRS and WRS were established concurrently and identical with respect to parental batch, aliquot volume, storage container and conditions, the qualification data obtained for PRS are applicable to WRS as well. The history of reference standards previously used is considered adequately described and comparability throughout development has been demonstrated. The primary and working reference standards are considered properly qualified and fit for purpose. The reference standards are requalified annually according to standard operating procedures.

A strategy for introducing new working reference standards has been outlined. In order to ensure continuity of the reference standards over time, the selection of parental batches for a new working reference standard will be based on the evaluation of the closeness of the quality attributes to the primary reference standard based on release data and extended characterisation results, including side-by-side testing of the new working reference standard with the primary reference standard for purity, protein content and potency. The strategy in place for introducing new working reference standards is considered appropriate.

Stability

The applicant proposed a shelf-life of 36 months for the active substance manufactured at the Lonza Slough and Lonza Tuas sites, based on stability studies performed in accordance with the ICH Q5C.The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for the identity, safety and some process-related impurities. The stability studies included primary batches (PPQ batches) and supportive batches (clinical batches produced by previous process versions) manufactured at both sites. Batches were placed on long-term storage, accelerated storage and stressed storage conditions. Additional stability data were provided. Available long-term stability data from primary batches showed a stable active substance over 18 months for the representative PPQ batches and 24 months for the supportive and 36 months for the clinical batches (former processes) using the tested stability-indicating methods.

Based on the available data for representative batches, a stability shelf-life of 18 months is acceptable for the active substance.

The stability of the active substance was, moreover, evaluated upon freeze/thaw (F/T) cycles using two representative batches from either of the manufacturing sites. Given that no changes were found in the critical quality attributes after several F/T cycles at the long-term storage condition, it was concluded that the active substance quality was not compromised by this amount of F/T cycles.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed out-of-specification (OOS) is proposed.

In conclusion, the stability results indicate that the active substance is sufficiently stable over the acceptable shelf-life of 18 months, in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

Efgartigimod alfa finished product is a colourless to slightly yellow, clear to slightly opalescent sterile, preservative-free, concentrate for solution for infusion. Each vial of 20 mL contains 400 mg of efgartigimod alfa. The composition of efgartigimod alfa finished product is presented in the dossier.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. An overfill of 0.6 ml is added to ensure the withdrawal of 20.0 ml. There is no overage in the efgartigimod alfa finished product.

Efgartigimod alfa is formulated at a target concentration of 20 mg/mL during active substance manufacture in sodium phosphate, sodium chloride, L-arginine, polysorbate 80, water for injections and further processed into finished product without changes to the qualitative or quantitative composition. No novel excipients or excipients of human or animal origin have been identified. Compatibility of active substance with the excipients is considered demonstrated.

Pharmaceutical development

The pharmaceutical development approach was based on the following elements: definition of a Quality Target Product Profile (QTPP), identification of potential 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 the definition of the quality control strategy.

The formulation step takes place during the active substance manufacture and the active substance and finished product formulations are identical. The formulation of efgartigimod alfa has remained unchanged throughout the entire non-clinical and clinical development. The protein concentration of 20 mg/mL was initially selected, being a typical concentration for monoclonal antibodies. The initial formulation development was performed in a two-step study: pH screen study and excipient study.

In addition, the results of the performed freeze/thaw study demonstrated that there was no impact on product quality attributes after several freeze/thaw cycles, confirming the suitability of the formulation to withstand freeze/thaw stress.

Parameter ranges have been evaluated in lab-scale studies (mainly with placebo), followed by a full-scale batch (also placebo). A multi-stage risk-based approach has been taken to establish the process control strategy using failure mode effect analysis (FMEA). Overall, the proposed sets of process and release controls are reasonable. The overview linking CQAs/CPPs, characterisation studies and proposed controls (link between PAR/NOR/acceptable ranges for CPPs) has been adequately described. During the assessment, the applicant was requested to revise the classification of the process parameters as CPP and non-CPP, in line with ICH Q8 recommendations.

The finished product process development is presented in sufficient detail. The process development has consisted in increasing the batch size and minor adjustments in parameter ranges to ensure facility fit. During the development the production was transferred to another manufacturing site. A bridging study was presented comparing a batch of finished product from each manufacturing site produced with the same active substance. Release sampling and stability sampling including general characteristics (appearance, protein content, pH, particles and osmolality), purity and charge variants, size variants and potency at both long-term and accelerated conditions have been compared. The results demonstrate comparability between the finished product batches manufactured by the two sites.

Container closure system

The container closure system for efgartigimod alfa finished product consists of a 20 ml Type I glass vial which is stoppered with a 20 mm bromobutyl rubber stopper and sealed with an aluminium crimp seal equipped with a tamper evident white polypropylene flip-off cap. The primary packaging components vial and stopper are of compendial quality (Ph. Eur.). Specifications and technical drawings with critical dimension have been submitted. The container-closure system is suitable for the finished product, as documented by stability data. The integrity of the container closure system under the applied stoppering and capping conditions has been verified.

Comprehensive extractables and leachables studies have been performed on the container closure components (CCS). The results showed that there is no safety concern linked to the selected CCS for the efgartigimod alfa finished product. The applicant also committed to continue to monitor samples stored at the long-term temperature condition of +5°C up to the 60 months time point and to report any result above the toxicological threshold and any new identified leachable (Recommendation).

In conclusion, the information provided on the container closure system selected for storage of efgartigimod alfa finished product is adequate and the system is considered suitable for the purpose.

In-use compatibility

Prior to administration, efgartigimod alfa concentrate for solution for infusion is to be diluted in 0.9% (w/v) sodium chloride. An in-use compatibility/short-term stability study was performed to demonstrate the compatibility of efgartigimod alfa concentrate for solution for infusion with 0.9% (w/v) sodium chloride, the administration procedure and administration auxiliary materials. Physico-chemical compatibility of efgartigimod alfa concentrate for solution for infusion diluted in 0.9% (w/v) NaCl is proven with a wide range of infusion bags and infusion lines over the defined time period. The results of a microbial post-dilution hold study observed no growth in the diluted product for any of the microorganisms tested. These results were concluded to support storage of the diluted finished product in the infusion bag for up to 24 hours at +2°C to +8°C following dose preparation. Additional data have been provided and based on the extrapolation of the microbial data at ambient temperature, applicant's claim that the infusion should be completed within 4 hours after removal of the diluted product from the refrigerator is considered justified.

Manufacture of the product and process controls

The efgartigimod alfa finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP.

A process flow diagram for the manufacture of efgartigimod alfa finished product is provided in the dossier. Detailed descriptions of the manufacturing steps are presented. A batch formula has been provided for the intended commercial batch size range for efgartigimod alfa finished product.

The finished product manufacturing process is standard and consists of thawing of the active substance, pooling and bioburden reduction filtration, sterile filtration and aseptic vial filling, stoppering and capping, visual inspection and secondary packaging and storage. The final composition of efgartigimod alfa finished product is identical to that of the active substance. No further compounding or dilution is performed during the finished product manufacturing process. There are no reprocessing steps and no intermediates in the finished product manufacturing process.

The critical steps in the efgartigimod alfa finished product manufacturing process are listed and the process controls are categorised as process parameters or as in-process controls and tests.

Maximum process times are defined to control time of active substance thawing, thawed active substance storage, bioburden reduction filtration, storage of bioburden filtered bulk active substance, sterile

filtration and filling and visual inspection. The processing times and holding times have been justified by the process validation studies.

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

The PPQ was performed in 3 campaigns each of 3 commercial scale batches: Campaign 1 and 2 with active substance from Lonza Slough and Campaign 3 active substance from Lonza Tuas. The PPQ protocol specifies relevant tests in addition to the defined controls.

The submitted data demonstrate that the process is generally well controlled, with little variation in the reported results, which were all within defined limits.

Process hold times have been challenged at the different steps, results demonstrate that quality is not affected. The challenges were primarily conducted on the batches with active substance from Lonza Slough and verified on 1 batch with active substance form Lonza Tuas. The approach is acceptable. Even if prolonged, the proposed hold time of the unsterile bulk finished product is considered acceptable as the solution has been filtered to reduce bioburden and is considered to be in control from a microbiological aspect.

Equipment, utilities and sterilising processes were adequately qualified prior to the PPQ including cleaning of equipment, depyrogenation of vials, autoclaving and aseptic processing media fill. A product specific filter validation, including bacterial retention, supporting the proposed processing limits was provided.

Transport studies covering the transport to the distribution warehouse was provided. The transport studies are performed according to relevant ISTA and ASTM standards and justifies the temperature and the integrity of the packaging during the transport. The potential impact of transport towards the product quality of efgartigimod alfa has also been studied. The results are considered acceptable.

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

Product specification

The proposed finished product release and shelf-life specifications for the efgartigimod alfa finished product are presented in the dossier. The parameters included in the finished product specification are found adequate to control the quality of the efgartigimod alfa finished product at release and shelf-life. The release specification includes general tests (visual appearance - colour, clarity and visible particles), osmolality, extractable volume, sub-visible particles, protein concentration, pH, identity), potency, purity, polysorbate 80 concentration and safety The same parameters with the same applicable limits are tested during shelf-life.

Tightening of the acceptance criteria was requested during the assessment for several parameters.

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

No new product-related impurities are seen in the finished product. As there are no new excipients added during the manufacture of the efgartigimod alfa finished product, the impurities present or potentially present in the finished product are considered the same as those identified and controlled in the active substance.

Elemental impurities were evaluated according to ICH Q3D. A detailed description of this risk assessment, as well as the elemental impurity analysis performed on 3 PPQ finished product batches, are included. It

is concluded that the overall risk of a potential release of elemental impurities into the efgartigimod alfa finished product is low and no specific control is considered necessary. This conclusion is agreed.

A risk assessment to evaluate the potential for nitrosamine formation and/or contamination during the manufacturing process of efgartigimod alfa finished product was performed and a summary presented in Module 1. The investigation included the active substance and excipients, water sources, primary packaging materials, processing aids with direct product contact, as well as the manufacturing equipment and the equipment cleaning process. Due to the design of the manufacturing process as well as the quality systems applied, the overall risk of a potential release of nitrosamines into the product during production is evaluated as low. The evaluation of the risk of nitrosamine is considered acceptable and no specific control is considered necessary.

Extractables and leachables studies performed on the bioburden reduction and sterile filtration filter used in finished product manufacturing are presented and discussed. The compounds identified by HPLC-MS are associated with the filter manufacturing process or related to the filter sterilisation process. Components of the filter device have been previously tested and were found to be non-toxic. This conclusion is agreed.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The compendial methods are performed in accordance with the current Ph. Eur. monographs, with the exception of the test for sub-visible particles that is performed according to Sub-visible Particles USP <787> monograph. The applicant has confirmed that USP <787> is interchangeable with the Ph. Eur. monograph on sub-visible particles. This approach is considered acceptable.

The tests for osmolality, extractable volume, visible and sub-visible particles and safety of efgartigimod alfa finished product are finished product specific methods. Tests for appearance, protein concentration, pH, identity, potency, purity and polysorbate 80 concentration are also performed on the active substance. These tests are described and validation data presented in the respective active substance sections. Finished product and active substance formulations are the same and no further processing is performed prior to vial fill. Therefore, the methods are concluded to be also validated for finished product testing. This approach is considered acceptable.

Batch analysis

Batch analysis data are presented for several PPQ batches derived from Lonza Slough active substance and from Lonza Tuas active substance. The batch data presented complies with the finished product specification and demonstrates manufacturing consistency.

Reference materials

See active substance section on Reference materials.

Stability of the product

The applicant proposed a shelf-life of 36 months at +5°C ± 3°C for the finished product. The stability studies were performed on primary and supportive batches stored 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), in accordance with the ICH Q5C.

The primary batches included PPQ batches based on active substance sourced from Lonza Slough, together with PPQ and clinical batches based on active substance sourced from Lonza Tuas. The

supportive stability batches included clinical batches produced by previous process versions at the commercial or clinical manufacturing site with active substance from either the Tuas or Slough site. Available long-term stability data from primary batches showed that the tested critical quality attributes of the finished product were stable and within the shelf-life acceptance criteria. This was supported by 18-36 months of stability data from supportive batches, which demonstrated a comparable and stable profile of the finished product.

The degradation pattern of the finished product was observed from stability studies using primary and supportive batches stored under accelerated and stressed conditions. The primary degradation pathways were identified for all the tested batches. The extrapolation of the stability data from finished product batches manufactured with active substance coming from former processes to the commercial finished product batches is not endorsed.

During the assessment, additional long-term stability data was provided for 18 months at 2°C-8°C for finished product batches representative of the commercial process. In addition, long-term stability data at 24 months at 2°C-8°C was provided for the initial finished product batches which is not considered representative of the commercial process. Furthermore, long-term stability data at 12 months at 2°C-8°C was provided for the primary batches. Based on the additional stability data provided for finished product batches representative of the commercial process, only a finished product shelf-life of 18 months at 2°C-8°C is acceptable.

The photosensitivity of the finished product was evaluated from a representative clinical batch placed into a photostability study performed in accordance with the ICH Q1B. Since changes were detected in a subset of critical quality attributes upon light exposure, which was not seen upon shielding of the finished product in its secondary packaging, the finished product was recommended to be stored in its outer carton to protect it from light. This is considered satisfactory.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed OOS is proposed. Furthermore, as part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

Based on available stability data, the shelf-life of Vyvgart 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. For the diluted solution, the chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately.

Adventitious agents

Non-viral adventitious agents

No animal or human-derived raw materials were used during generation of the efgartigimod alfa production cell line or establishment and storage of master and working cell banks. No microbial agents (bacteria, mycoplasma or fungi) were detected in any of the cell banks used for manufacture of efgartigimod alfa, including master cell bank and working cell bank.

Apart from the CHO derived production cell line, no animal or human derived raw materials are used in the manufacture of efgartigimod alfa. During routine manufacture, appropriate measures are in place for controlling the risk of contamination with non-viral adventitious agents, including the facilities and equipment used, filtration of process solutions through sterilising grade filters prior to use and performing in-process controls for bioburden, endotoxin and mycoplasma.

The efgartigimod alfa active substance and finished product are tested for absence of fungi and bacteria and level of endotoxin at release, using compendial methods (Ph. Eur.). Based on the information provided, the Vyvgart product is considered safe with regard to non-viral adventitious agents.

Viral adventitious agents

The MCB, WCB and EOPC banks were tested negative for the presence of a comprehensive panel of adventitious viruses. Testing for endogenous retroviruses was performed in accordance with ICH Q5A with only non-infectious RVLP known to be expressed in CHO derived cell lines, being detected.

Testing of unprocessed bulk harvest for viral contaminants is conducted, using *in vitro* assay for adventitious viruses. Results have been provided from unprocessed commercial scale bulk harvest batches, verifying the absence of adventitious viral contamination. The same batches were tested for determination of the RVLP level, which was used for calculation of endogenous RVLP safety factors. The viral clearance capacity of the efgartigimod alfa active substance purification process was evaluated by conducting viral clearance studies, using qualified scale down models in accordance with ICH Q5A. The scale down procedure is considered acceptable and the scale down model representative of the commercial scale. Orthogonal purification steps were adequately evaluated.

Model viruses were used for the virus validation. The selected model viruses represent a wide range of particle size, genome-type and degree of resistance to physico-chemical treatments.

Both unused and used resin were validated for virus clearance capacity and were found to be equally effective up to multiple runs, corresponding to the validated commercial scale resin lifetime.

Cumulative log reduction (CLR) values were calculated. From these, a safety factor has been determined This is considered a low and acceptable risk.

Conclusion

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi and viruses is considered well contained, based on selection of safe raw materials, demonstration of absence of adventitious (and endogenous) agents in cell banks, testing at relevant stages of the process and finally the substantial virus clearance capacity, demonstrated for the efgartigimod alfa purification process at both active substance manufacturing sites.

GMO

Not applicable.

2.4.4. 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.

In summary, from a quality point of view, a positive CHMP opinion of the quality part can be recommended.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the ongoing long-term leachable study. This point is put forward and agreed as recommendation for future quality development.

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The applicant is recommended to continue to monitor samples stored at the long-term temperature condition of +5°C up to the 60 months time point and to report any result above the toxicological threshold and any new identified leachable.

2.5. Non-clinical aspects

2.5.1. Introduction

Rat, rabbit and cynomolgus monkeys were selected as relevant species for the nonclinical safety evaluation of efgartigimod IV. Suitability and relevance of the species were demonstrated via in vitro binding to the FcRn target and in vivo pharmacokinetic/pharmacodynamic (PK/PD) studies (all species) in addition to tissue binding studies (cynomolgus monkey). Two pharmacologically relevant species (rat and cynomolgus monkey) were used for the short-term (up to 4-week duration) general toxicology studies, and cynomolgus monkey was used as the sole toxicity species for longer term toxicity testing, in line with the principles of ICH Topic S6 Addendum, based on the highly similar binding properties of efgartigimod to cynomolgus monkey and human FcRn, respectively. Reproductive toxicity studies were conducted in rat as the rodent species and rabbit as the nonrodent species (ICH Topic S5 (R3)). The IV route was used in all studies, which is the intended route of administration in humans, and all pivotal studies were conducted according to Good Laboratory Practice (GLP) standards.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

A literature review has been submitted to describe the expected mode of action of efgartigimod as a FcRn antagonist. The main findings are described below. FcRn is predominantly expressed in endothelial cells and cells of myeloid lineage and contribute to the homeostasis of IgG. FcRn plays a major role in the recycling of all IgG subtypes (IgG1, IgG2, IgG3, IgG4) back into the circulation by preventing uptake into lysosomes of the IgG-FcRn bound complex, thus rescuing IgGs from lysosomal degradation. In addition, FcRn transcellularly transports IgGs into tissues (transcytosis). Efgartigimod functions as a FcRn antagonist, and the blocking of FcRn results in enhanced IgG degradation, which is expected to lead to an increased clearance of IgG autoantibodies. The neuromuscular junction (NMJ) disorder, general myasthenia gravis (gMG), is characterized by pathogenic autoantibodies to postsynaptic muscle endplate components (the acetylcholine receptor (AChR), muscle-specific kinase (MuSK) or low-density lipoprotein-related protein 4). These IgG autoantibodies inhibit efficient signal transduction between

neurons and muscles and, hence, induce muscle weakness. By reducing the concentration of circulating IgG autoantibodies, it is expected that efgartigimod could alleviate signs and symptoms in severe autoimmune diseases such as gMG.

Efgartigimod was investigated in two in vitro assays (enzyme-linked immunosorbent assay (ELISA) and via surface plasmon resonance (SPR) measurements) to determine the affinity to human FcRn. The pH-dependence of FcRn-binding was investigated at both pH 6.0 and pH 7.4 as IgG is taken up by cells and binds to FcRn at relatively acidic conditions in the early endosome. The increased affinity at acidic pH may be relevant in intracellular environment, but not for extracellular/plasmatic media where so low pH is not possible to reach. Binding of efgartigimod investigated in both assays demonstrated a higher affinity for FcRn compared to the wild-type Fc counterpart at both neutral and acidic pH (100-fold at pH 6.0). No wild-type Fc binding was detected at pH 7.4 whereas high affinity for FcRn was observed for efgartigimod at both pH values, which increased with decreasing pH.

The cross-reactivity to non-human species was investigated using SPR measurements to assess the relevance of various species for pharmacologic and toxicologic analysis of efgartigimod. It was re-established that increased FcRn binding could be associated with decreasing pH in rodents. In cross-reactivity studies efgartigimod showed higher affinities for rodent FcRn compared to human FcRn affinities (mice: 35-fold/>10-fold at pH 7.4/6.0; rats: ~5-fold at pH 7.4) whereas affinities for cynomolgus FcRn were comparable to human FcRn affinities. Affinity for rabbit FcRn at pH 7.4 was 10-fold lower compared to human FcRn affinity. The findings of the SPR measurement study were confirmed in another cross-reactivity study using FcRn-binding ELISA at both acidic and neutral pH for mice, rats and cynomolgus monkey while rabbit FcRn was not included.

In selecting the most optimal biopharmaceutical format, efgartigimod was chosen over IVIg, a full-length IgG1 antibody with ABDEG mutations (ABDEG-hIgG1) and another Fc fragment with NHance mutations (HN-Fc) due to considerations regarding highest achievable affinity for FcRn and consequent reduction of IgG levels as well as risk of potential nonspecific binding.

Several in vivo studies were conducted in order to evaluate the level of reduction of circulating IgG levels induced by efgartigimod in different animal species.

Mice appeared to be most sensitive to efgartigimod treatment compared to rats in a non-GLP IV single dose study, as a reduction in IgG was already observed at 2 mg/kg whereas a reduction only occurred in rats at 20 mg/kg and above (tested dose levels 2, 20 and 100 mg/kg, study ARGX-NC-076). Saturation of reduction was observed in mice at 20 mg/kg. The results in rats were corroborated by a GLP IV repeat dose study where reduction of IgG titers was observed at 10 mg/kg and above (tested dose levels 10, 30 and 100 mg/kg, study LPT33981). It was further noted that dose-dependency was not observed in the rats and that it appears that the maximal PD effects is achieved at 10 mg/kg with a peak reduction 7-13 days after treatment initiation.

In rabbits, administration of 20 and 100 mg/kg efgartigimod was able to induce a reduction of endogenous IgG levels after a single-dose administration (tested dose levels 2, 20 and 100 mg/kg, study ARGX-NC-043) with a peak reduction after 7 days. However, a decreased in vivo efficacy was observed in rabbits compared to mice and rats, which also correlates with the lower affinity of efgartigimod for rabbit FcRn at physiological pH observed in in vitro studies. A higher reduction in IgG levels were demonstrated in pregnant rabbits after repeated dosing of 10, 30 and 100 mg/kg (study ARGX-NC-065), for which a reduction of IgG levels was also noted in the control group. However, this appeared to be due to the higher maternal-fetal transfer of IgG at the end of gestation.

In cynomolgus monkeys, dose levels from 20 mg/kg and above enhanced the clearance of tracer IgG and endogenous IgG (tested dose level 0.2, 2, 20 and 200 mg/kg) after IV single dose administration (non-GLP, study ARGX-NC-078). A (near) maximal PD effect was obtained at doses starting from 20

mg/kg. The effects of repeated dosing versus single infusion were investigated in cynomolgus monkeys (study ARGX-NC-078). It was shown that daily infusion of efgartigimod (20 mg/kg, 3 h IV infusion) and single infusion every 4 days (q4d) resulted in similar reduction levels in the initial phase of the study, though q4d administration resulted in longer reduction of serum IgG levels. Several GLP compliant single dose and repeat dose studies in monkeys demonstrated similar results as regards reduction in IgG levels with peak levels after 7-15 days after treatment initiation. In the monkey studies, some dose dependency was demonstrated unlike in the other species, as the PD effect appeared to be more pronounced in the high-dose groups.

Common for all animal studies including a recovery phase, it was noted that reductions in IgG levels had normalized at the end of the recovery period in all animals.

ADA formation was observed in two of the in vivo PD effect studies in cynomolgus monkeys but was not observed in the other tested species in the short-term duration of the studies. ADA formation resulted in exclusion of data measured from day 18 and day 24, respectively, in the two studies. However, this is considered acceptable by CHMP as it appears that the maximum IgG reduction occurs earlier (day 7-15) in monkeys, and it is considered that the ADA formation does not significantly affect the conclusion of the short-term PD studies. In the longer studies however (notably the 26-week repeat-dose toxicity study in monkeys), signs of waning PD effects were seen after a few weeks in the low-dose group and, to some extent, in the mid-dose group.

It is noted that during drug development, the producer cell line was exchanged by another producer cell line, which is being used to produce the active pharmaceutical ingredient of efgartigimod in the commercial lots. A PK/PD study was conducted in cynomolgus monkeys to evaluate potential differences in PK and PD between the batches produced by both cell lines (study ARGX-NC-092). The monkeys received an IV administration of 20 mg/kg and data was compared to an earlier study assessing the same dose (study ARGX-NC-078). IV treatment with efgartigimod that originated from either clone showed similar IgG reduction (~50%) and maximum PD effect was reached after 5 to 7 days with similar results for all groups. In conclusion, the PK/PD results obtained with the two batches appear to be similar and the exchange during drug development is not considered to pose a problem for the nonclinical dossier. Similar results were obtained in the dedicated PK studies confirming the similarity of the two batches.

The effect of efgartigimod was investigated in relevant animal models of disease in mice and rats. Myasthenic features were induced in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice via infusion of patient IgG (MuSK-MG patient IgG) (study ARGX-NC-079). It was demonstrated that efgartigimod treatment led to significantly lowered anti-MuSK antibodies levels which correlated with stabilization of the mice in functional tests, e.g. of the grip strength and a normalization of the hanging time in an inverted mesh test. Further, ex vivo tests assessing contraction force of the diaphragm in order to evaluate the condition of muscle contraction were conducted. Overall, it appeared that efgartigimod was able to improve the induced condition in the MG mouse model and prevented or reduced the progressive body weight loss and myasthenic muscle weakness induced by MuSK-MG patient IgG4. The conclusion from the mice studies were confirmed in a rat study using a passive transfer model for AChR-MG (ARGX-NC-080). Efgartigimod reduced rat IgG levels (up to 50% reduction versus baseline levels within 48 hours after first injection) and in addition improved the clinical score and grip strength.

2.5.2.2. Secondary pharmacodynamic studies

The affinity of efgartigimod for Fc gamma receptors (FcγRs) or C1q was investigated in vitro in order to elucidate the potential risk for inducing antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-

dependent cellular phagocytosis, and complement-dependent cytotoxicity (CDC). Efgartigimod was investigated in an ELISA assay including FcγRI (CD64), FcγRIIa (CD32a), FcγRIIb (CD32b), FcγRIIIa (CD16a), and C1q against a wild- type Fc fragment (study ARGX-NC-074). Impaired binding for both FcγRII receptors was observed while efgartigimod showed a 3.2-fold lower affinity for FcγRIIIa compared to the wild-type Fc fragment. Binding to the high-affinity FcγR (FcγRI) as well as C1q was both reduced by 1.5-fold compared with the wild-type Fc fragment in the in vitro assay. In addition, efgartigimod lacks the antigen-binding regions (Fab fragments), which mediates cross-linking after target engagement. Taken together with the reduced affinity for FcγRs and C1q compared to a wild-type Fc fragment, it appears unlikely that efgartigimod will directly activate the ADCC and CDC pathways. To further elucidate the potential untargeted binding of efgartigimod, the activation of NK cells was investigated in vitro. Efgartigimod activated 0.5% of NK cells after the incubation period, which was similar for the wild-type Fc fragment, whereas the positive control activated 9-12% of the NK cells after the incubation period. This further substantiates that efgartigimod is unlikely to lead to FcγR cross-linking on immune cells or induce nontargeted immune cell activation.

Efgartigimod is specifically designed to block the recycling of IgG through binding to the FcRn molecule and should thus not interfere with other Igs, such as IgA and IgM. Though albumin also binds to the FcRn molecule, the binding site is distinct from that of IgG, and efgartigimod should thus not influence the recycling process for albumin. To elucidate the potential effect of efgartigimod on levels of IgA, IgM and albumin binding kinetics were investigated in vivo in non-GLP and GLP studies in rats and monkeys as part of the PD and toxicological dossier, to show that efgartigimod does not affect the circulating levels of IgA, IgM and albumin. Overall, the studies showed that single- and repeat-dose administration of efgartigimod in doses of up to 100 mg/kg in rats and up to 200 mg/kg in cynomolgus monkeys did not influence IgA, IgM, and albumin levels. It should be noted that albumin levels were increased up to 15% in all groups dosed with efgartigimod in the 4-week toxicity study in rats. It was however assessed that the relatively small increase in albumin is not likely to be of clinical concern, as the effect was not observed in monkeys or in clinical studies.

2.5.2.3. Safety pharmacology programme

Safety pharmacology assessments were performed as part of the GLP-compliant general toxicity studies in rat and cynomolgus monkeys and as part of a GLP-compliant PK and safety pharmacology study in cynomolgus monkey. No significant findings were reported concerning safety pharmacology parameters in any of the studies at efgartigimod doses up to 100 mg/kg administered q2d or q7d.

The potential effects of efgartigimod on the cardiovascular system was evaluated by measurements performed on the monkeys included in the toxicology studies. In the ICH S7A safety pharmacology guideline, it is stated that the "*effects of the test substance on the cardiovascular system should be assessed appropriately*" and further that "*data from unrestrained animals that may be chronically instrumented for telemetry, …. are preferable to data from restrained or unconditioned animals*". However, in the studies performed, the recordings were made while the animals were fixated to a dosing chair. As a consequence, the mean heart rates found prior to dosing were approximately twice that typically found in resting cynomolgus monkeys (Engwall et al., 2021), reflecting that the animals were stressed during the recordings. Similarly, the mean blood pressure was markedly higher than what is typically found using telemetry. This limits the usefulness of the studies in terms of identifying a potential effect of the product on the cardiovascular system. Severe effects would likely be detected, but milder effects on for instance blood pressure might not be found. However, the molecule *per se* raises no concerns regarding cardiovascular safety, and no cardiovascular safety signals were observed in the clinical studies conducted.

Regarding the respiratory parameters, the recordings were made while the animals were fixated to a dosing chair in the pivotal monkey safety pharmacology study. As a consequence, the mean respiration rates found prior to dosing were 33 to 43 (depending on the group), which is higher than the rate of 25-30 typically found in telemetered (unstressed) cynomolgus monkeys (Trefry et al., 2021). For this reason – and because of the small number of animals – mild signals could be missed. However, no signals were observed in any of the non-clinical studies and respiration-related side effects (other than upper respiratory tract infections) were not observed in humans in the phase III study (ARGX-113-1704).

Effects on the central nervous system were evaluated by observations and examinations made according to a standardized grid in the pivotal monkey study. No significant findings were made. The tendency to decreased startle response in the high-dose group was comparted to the control group by comparing group means. However, looking at day 1 and day 29 data in combination, 6 of 8 tests performed after dosing in control animals showed a normal startle response, while only 1 of 8 tests performed after dosing in the high-dose group showed a normal startle response – the remaining 7 tests showed no response. However, other very similar tests showed no concern and no changes in behaviour were noted at cage-side observations during general repeat-dose toxicity studies in rats and cynomolgus monkeys and was concluded not to be biologically relevant.

2.5.2.4. Pharmacodynamic drug interactions

Due to the mode of action of efgartigimod, potential interactions with therapeutic IgGs may occur, which may be influenced by the spacing of dosing of the two therapies. The potential interaction between efgartigimod and IVIg was investigated using a human FcRn transgenic mice (Tg32 mice) model where the effect of either simultaneous IVIg/efgartigimod (20 mg/kg) administration or initial efgartigimod administration followed by IVIg treatment (2 days later) were studied. Treatment with IVIg did not affect the PK profile of efgartigimod in any of the studies. Efgartigimod on the other hand affected the exposure of IVIg and tracer antibodies in line with its intended mode of action as the level of IgG was reduced after simultaneous or subsequent administration. The potential interactions of efgartigimod have been addressed in the SmPC section 4.5.

A GLP-compliant nonclinical T-cell Dependent Antibody Response (TDAR) safety study in cynomolgus monkeys was performed to study potential interaction with vaccines and the potential effect on active immunity of efgartigimod. The study showed that mechanisms of responses to vaccines and vaccine boosters appears to remain intact under efgartigimod treatment, though lowered levels of antigen-specific IgG need to be considered during exposure to efgartigimod. This is addressed in section 4.4 of the SmPC. All parts of the vaccine response are fully restored after treatment cessation.

2.5.3. Pharmacokinetics

The GLP compliant bioanalytical program was considered by CHMP to be extensive and well-designed. ELISA methods were used in all studies measuring in serum. Precision, accuracy, dilution integrity, selectivity and stability appeared to be adequate for a ligand binding assay.

The method for determination of efgartigimod in urine was based on the same ELISA principles as for serum. In the first instance, the analysis of urine for efgartigimod was exploratory, hence validation was not considered necessary. This is agreed by CHMP. A qualified method was developed for urine samples collected in 26-week toxicity study in monkey.

An assay for measuring efgartigimod in cynomolgus monkey serum samples in the GLP-compliant 11-week TDAR study in cynomolgus monkeys was validated, showing an adequate precision, accuracy,

dilution integrity, selectivity and stability as well as incurred sample reanalysis. Further, an ELISpot assay for determination of IFNγ excretion in Non-Human Primate PBMCs appear to be adequately validated.

Several GLP-compliant validated ADA assays in the serum were developed to support the measure of ADAs in nonclinical safety studies in rats and cynomolgus monkeys. The first assay was in the simple bridging ELISA format in which both a screening and a confirmatory phase was used. However, this was not optimal for repeat-dose studies due to poor drug tolerance. Instead, a format was employed in order to elute antibody bound efgartigimod from the sample prior to detection of the antibody. This alternative procedure substantially improved the drug tolerance of the assay, so a confirmatory analysis was not necessary. Otherwise, the ADA assays appear to be appropriately validated and used in studies fit for their purpose.

The efgartigimod serum kinetics profile over time has been studied in single- and repeat-dose studies in mouse, rat, rabbit, and cynomolgus monkey. The PK evaluation focused on data obtained from studies in cynomolgus monkey due to the similarity of efgartigimod binding properties to cynomolgus monkey and human FcRn. Methods for detecting efgartigimod in serum in support of nonclinical studies used an identical setup, where a capture reagent was employed that targeted an efgartigimod specific epitope. The ligand binding assay used for the detection of efgartigimod in urine (exploratory analysis) differed from that used for serum samples but was adequate for use in that matrix. Assays in support of GLP-compliant nonclinical safety assays were validated according to relevant guidelines, and gaps that were identified were investigated and were found to not have influenced study results. An identical setup was employed to develop and validate PK assays in support of clinical trials, simplifying subsequent comparisons. Validated ADA assays were used in support of the general toxicity studies. No aberrant TK profiles were noticed in reproductive toxicity studies and therefore, ADA sample analysis was not performed in those studies. Efgartigimod showed largely similar PK in all species tested; some minor differences were noted, likely due to slight differences in FcRn binding properties. At the studied IV doses, including doses higher and lower than those intended in humans, PK parameters were dose linear and did not change over time. There was no or minimal accumulation and no sex difference. Disposition of efgartigimod is expected to follow the principles that govern those of mAbs. Special considerations arise from the smaller size and the higher affinity to FcRn compared to most therapeutic mAbs; a property which may lead to (partial) sequestration of efgartigimod to FcRn expressing compartments and organs with permeable capillaries (which does not include privileged compartments such as brain and testis). Cynomolgus monkey was identified as the most relevant species to study PK and consequently characterization of PK parameters focused on data obtained in this species. In brief, the following was found:

(i) two half-life phases could be distinguished, a shorter t½,eff of 19 to 45 hours and a longer terminal elimination phase that represented a minimal part of the exposure only, did not contribute to accumulation and was not pharmacologically relevant;

(ii) the systemic clearance (CL) was 2 to 4 mL/h/kg and therefore higher than that typically seen for mAb pharmaceuticals, and that was constant over different doses and time;

(iii) a volume of distribution (Vss) of 126 mL/kg was determined, indicating distribution into other compartments in addition to plasma (as mentioned above). The longer elimination phase seen in several nonclinical studies was speculated by the Applicant to reflect efgartigimod that is released from the FcRn and becomes measurable once serum concentrations fall below sub-pharmacological level.

Regarding the AUCs (0 to168 hours) used to estimate exposure ratios to humans, these were often determined with too few datapoints. For example, in the pivotal 26-week monkey study, only few data points were available in the week after dosing – for example none between 24 and 168 hours. As the (linear) trapezoidal method used by the applicant to calculate AUCs does not capture the exponential

decline in concentrations, (too) few datapoints will lead to an overestimation of the AUCs and thereby the exposure ratios (see further discussion on this in the toxicology section below).

In all species and all major studies, several animals developed anti-drug antibodies – typically starting between day 7 and 15 – but the impact on the studies was minimal. In the two low dose groups of the pivotal 26-week toxicology study, there were signs of waning PD effects and a few animals showed markedly reduced exposure and had to be excluded from TK analysis due to aberrant concentration-time profiles. In the high dose group (i.e. the group defining the NOAEL), however, a full PD effect and a sustained high exposure was found throughout the study. The very slow elimination in the recovery period meant that the compound was still found in samples from 9 of the 12 efgartigimod-treated animals at the end of the 8-week recovery period. However, the concentrations were low and a full recovery was seen regarding all parameters. Overall in the nonclinical studies, ADA were observed in all dose groups, with no dose relation, and no associated toxicology findings (albeit it could not be excluded that reversible findings in the 4-week repeat-dose toxicity study in the rat were immunogenicity-related, as discussed in the toxicology section). In the reproductive toxicity studies, consistent exposure was verified in all animals, and analysis of ADA samples was therefore not necessary. The development of ADA in nonclinical species is often observed for biotherapeutics and is not considered predictive for the effects in humans.

Efgartigimod is a protein, and lysosomal degradation after pinocytosis is expected to be an important pathway for elimination. In addition, renal excretion occurred at low levels. The PK of efgartigimod after IV administration has been sufficiently characterized in the relevant nonclinical species. No dedicated studies were submitted to investigate distribution and metabolism of efgartigimod, however, this is acceptable as the product is biotechnologically derived and is in accordance with the guideline ICH S6.

Distribution to other privileged compartments such as brain and testis has not been studied but effects are unlikely since monoclonal antibodies typically have a low blood to brain tissue ratio.

PK interactions of efgartigimod with co-administered small molecular drugs are not expected due to specific mode of action and degradation via other metabolism pathways than the CYP450 system. An influence on the PK behavior of mAb therapeutics or IVIg is however likely, which has adequately been described in the SmPC section 4.5.

2.5.4. Toxicology

Overall, all drug substance batches used in the toxicity studies were considered representative for efgartigimod batches used in the clinical trials. However, quantifiable endotoxin levels within the acceptance criteria were present in pilot batch P3179589 used for the extended single-dose study and the 4-week toxicity study in cynomolgus monkey. Due to the high dose-levels in both studies, total injected amounts of endotoxin became significant and likely contributed to findings in these studies. Active exposure was monitored in single- and repeat-dose general toxicity studies by measuring PD effects. The reduction of mean total IgG values in comparison to controls was confirmed in all treatment groups receiving efgartigimod at the selected doses. Antidrug antibodies (ADA) were monitored in the single and repeat-dose general toxicity studies in rats and cynomolgus monkeys. In general, ADA were only measurable at the end of the treatment period and not before study day 15, and often more during recovery. This and other observations suggest that the performance of the ADA assay used could be influenced by the presence of efgartigimod. Efgartigimod concentration was superior to established drug tolerance for the applied bioanalytic method, at least for a single cynomolgus monkey for which the drug concentrations remained above the drug tolerance level till the end of the recovery phase in contrast to other animals. However, this observation must be put into perspective because the bioanalytical method was validated for improved tolerance in the pivotal study (26-week toxicity in monkeys), and thus

reaching drug tolerance to a level higher than the concentration of efgartigimod. This suggests negligible interference in this pivotal study. Similarly, drug tolerance in rat samples was higher than efgartigimod measured serum concentration, supporting a low concern for interference.

No dose-relationship between the induction of ADA responses and efgartigimod treatment was observed and ADA, where present, did not impede the interpretation of data. The defined no observed adverse effect level (NOAEL) and associated exposure values were used to calculate an exposure margin in comparison to the human exposure (see section 3.2.4.6).

2.5.4.1. Single dose toxicity

In an extended single-dose IV toxicity study in cynomolgus monkeys, no efgartigimod-related adverse events were observed, resulting in a NOAEL of 100 mg/kg (the highest dose tested). The serum concentrations appeared to decline in two phases.

2.5.4.2. Repeat dose toxicity

In the 4-week repeat-dose toxicity studies, rats and cynomolgus monkeys were treated with efgartigimod every 48 hours (q2d; a total of 15 IV doses). These studies showed that efgartigimod was well tolerated and did not cause any efgartigimod-related adverse findings at doses up to 30 mg/kg q2d. Findings of minimal to slight Kupffer cell hypertrophy/hyperplasia seen in male and female rat liver at 100 mg/kg q2d were considered of uncertain relationship to treatment. Nevertheless, the NOAEL was established at 30 mg/kg q2d. In male and female cynomolgus monkeys in the 4-week repeat-dose study, slightly elevated serum alanine aminotransferase (ALAT) was seen additionally to hepatocyte cytoplasmic alterations and degeneration, and diffuse mixed inflammatory cell infiltrates in the liver at 100 mg/kg q2d. These changes were fully reversible within the 4-week recovery period. A NOAEL of 30 mg/kg q2d was defined in the report. The levels of endotoxin administered in this study exceeded general USP recommendations and likely influenced the findings. The TK data of the 4-week studies in rats or cynomolgus monkeys demonstrated that all efgartigimod-treated animals were consistently exposed to efgartigimod throughout the treatment period. In the pivotal 26-week toxicity study of efgartigimod, cynomolgus monkeys received IV infusions at doses of 0 (vehicle), 10, 30, and 100 mg/kg once every week (q7d; a total of 27 infusions per animal). Efgartigimod was well tolerated at all doses as determined by clinical signs, body weight, food and water consumption, ECG, circulatory functions, laboratory diagnostics, ophthalmological and auditory functions, organ weights, and bone marrow cellularity at any study dose level. Neither macroscopic nor microscopic efgartigimod-related changes were observed at the end of the 26-week treatment period or 8-week recovery period. Therefore, the NOAEL was established at 100 mg/kg q7d in the cynomolgus monkey. The TK data of the 26-week study in cynomolgus monkey demonstrated consistent exposure over the full treatment period, with exceptions of 4 and 2 animals in the low- and mid-dose group, respectively, where decreased efgartigimod serum levels were noted in conjunction with high ADA titers beginning on day 15. None of the animals were excluded from the toxicology assessment and the study data were considered valid at all dose levels. None of the high-dose animals were excluded from TK evaluation. The repeat-dose toxicity study of efgartigimod provided a NOAEL of 100 mg/kg q7d.

Reversible effects after administration of a pilot batch of efgartigimod in the cynomolgus monkey in two studies were not considered to be translatable to the human situation as the presence of endotoxins likely influenced study outcomes.

Overall, in the toxicology studies performed, there were no signals reported that would imply a safety risk that is translatable to humans. Reversible findings in the 4-week toxicity studies at high doses in rat and cynomolgus monkey were of uncertain relationship to the pharmacology of efgartigimod and in the

cynomolgus monkey likely associated with excessive levels of endotoxin present in the pilot batch of drug substance used. Administration of a single dose of ≥ 10 µg/kg LPS to cynomolgus monkeys has been found to result in increased levels of large unstained cells and ALAT (Picha et al., 2004). In a study, less endotoxin (approximately 3 ng/kg) were given per dose but were administered every other day for a total of 15 injections, which may have exacerbated responses. Elevated ALAT often reflects overt damage to hepatocytes and although information on liver histopathology after endotoxin/LPS exposure is lacking in the nonhuman primate in literature, overt hepatocellular damage is a well-recognized pathology in the rat dosed with LPS.

No safety signals were reported for the 26-week pivotal toxicity study in cynomolgus monkey. It should be noted, however, that the studies were not optimally designed to detect potential acute adverse effects on the cardiovascular system (see the safety pharmacology section). The pivotal 26-week toxicity study, applying a q7d dosing regimen, was considered the most relevant study to assess the safety margin for q7d dose regimen in human.

2.5.4.3. Genotoxicity

Efgartigimod is a biotechnology-derived product; thus, no genotoxicity studies were performed in line with guideline ICH S6.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted as

(i) the target of efgartigimod (FcRn) is not implicated in carcinogenesis

(ii) no findings were reported in the conducted toxicity studies that would imply a risk; and

(iii) no secondary pharmacology was identified.

As such, the lack of carcinogenicity studies is considered acceptable by CHMP.

2.5.4.5. Reproductive and developmental toxicity

Reproductive and development toxicity studies were conducted for efgartigimod given by IV bolus injection. The Segment 1 (fertility and early embryonic development) study in rats, Segment 2 (embryo-foetal development and maternal toxicity) studies in pregnant rats and pregnant rabbits as well as Segment 3 (pre and postnatal development in rats including maternal function) study in rats were designed in accordance with the ICH Topic S5 Guidelines. The TK data of the studies demonstrated consistent exposure over the full treatment period. All NOAEL values were established at the highest tested dose of 100 mg/kg/day A potential reduction in transfer of IgG from the mother to the foetus can occur due to FcRn inhibition across the placenta. This has been adequately reflected in section 4.6 of the SmPC.

2.5.4.6. Toxicokinetic data

The toxicokinetic data has been evaluated as part of the different non-clinical studies and are mentioned as appropriate in the sections above.

Based on the achieved serum concentrations in the nonclinical safety studies, margins of exposure were calculated. The pivotal 26-week toxicity, applying a q7d dosing regimen, was considered the most relevant study to assess the safety margin for q7d dose regimen in human. The animal to human

exposure multiples were estimated to be approximately 11- and 5-fold for Cmax and AUC, respectively in that study. CHMP considered that these exposure multiples are acceptable for a highly specific biotherapeutic like efgartigimod, dosed at full receptor occupancy, that shows no noticeable safety signals in nonclinical or clinical studies

2.5.4.7. Local Tolerance

Regarding the assessment of local tolerability of efgartigimod, CHMP concluded that the risk of a local intolerance reaction due to the efgartigimod formulation, containing sodium phosphate, sodium chloride, arginine, polysorbate 80, pH 6.7, when administered via IV infusion to patients can be considered low.

2.5.4.8. Other toxicity studies

Based on the general toxicology studies, the risk of unwanted activation of the immune system appears to be low. The structure of the efgartigimod molecule further points to a low risk for immunotoxicity, as efgartigimod lacks the Fab region, which is required for binding to effector molecules and furthermore, it is engineered to bind with high affinity to the human FcRn. Furthermore, a certain baseline level of IgGs is retained. The potential effect of efgartigimod on active immunity, e.g. in response to a vaccine, has not been investigated, however, this has been adequately addressed in the SmPC and RMP.

The active substance and drug product are generally well controlled at production level. The quantitative differences arising from the exchange in producer cell lines are considered sufficiently characterised in PD/PK studies in monkeys. Furthermore, potential process derived impurities are cleared to very low levels. Thus, no impurities have been identified that is of toxicological concern.

2.5.5. Ecotoxicity/environmental risk assessment

As per the EMA Guideline EMEA/CHMP/SWP/4447/00 corr 2, Section 2, no environmental risk assessment studies were performed which is considered acceptable by CHMP.

Efgartigimod is a monoclonal antibody which will be broken down by proteolysis, as such it will not alter the concentration or distribution of the substance in the environment. Therefore, efgartigimod is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Primary pharmacodynamic studies demonstrated that efgartigimod has an increased affinity for all tested nonhuman FcRn molecules, as compared with a wild-type Fc fragment. Also, it was demonstrated that the FcRn-efgartigimod binding profile is highly similar between cynomolgus monkey and human with what appears to be similar FcRn-binding kinetics as well as target tissues (endothelial cells and macrophages in intestine and spleen (also liver and kidney based on literature data)). Based on this, the cynomolgus monkey was selected as primary pharmacological and toxicological model, which is considered acceptable by CHMP.

The potential effects of efgartigimod on the cardiovascular system was evaluated by measurements performed on monkeys included in the toxicology studies and made while the animals were fixated to a dosing chair. As a consequence, the mean heart rates found prior to dosing were approximately twice that typically found in resting cynomolgus monkeys reflecting that they were stressed during the recordings. Similarly, the mean blood pressure was increased above resting levels. This limits the

usefulness of the studies in terms of identifying a potential effect of the product on the cardiovascular system. However, the molecule *per se* raises no concerns regarding cardiovascular safety, and no cardiovascular safety signals were observed in the clinical studies conducted.

The development of anti-efgartigimod antibodies (ADAs) was a general phenomenon in the animal studies. Findings made in the studies suggest that the prevalence of ADA could be underestimated in the presence of high efgartigimod concentrations. However, the influence on the validity of the toxicology studies was minimal as a clearing effect was only seen in a few animals, resulting in unaffected exposure throughout the key studies. Signs of an ADA-related effect was seen on the pharmacodynamic effects. Thus, the IgG-reducing effect of efgartigimod waned over time in the low- and mid-dose groups of the pivotal 26-week repeat-dose toxicology study in monkeys but in the high-dose group, no effect was seen.

The highest dose used in all key toxicology studies were 10 times higher than the dose planned in humans. Generally, this resulted in Cmax values being slightly higher than 10 times those found in humans. The fact that efgartigimod in some studies was given using a shorter infusion time (or even as a bolus) likely contributed to this. The relatively short effective half-life found in animals, resulted in AUCs showing a smaller safety ratio to humans (approximately 5). However, CHMP considered that these exposure multiples are acceptable for a highly specific biotherapeutic like efgartigimod, dosed at full receptor occupancy, that shows no noticeable safety signals in nonclinical or clinical studies.

None of the studies conducted regarding reproductive and developmental toxicity assessed the exposure of foetuses to efgartigimod and also, the possibility that blocking the FcRn receptor with efgartigimod will result in a general block of the transfer of maternal antibodies to the foetus was not addressed. The potential for efgartigimod to reduce the transfer of antibodies from mother to foetus has however been adequately reflected in section 4.6 of the SmPC.

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 is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* non-clinical pharmacology was conducted for efgartigimod, including in disease models, supporting the intended clinical use of efgartigimod. Nonclinical proof of concept as a Fc receptor (FcRn) antagonist mediating an increased IgG degradation appears well-established. Further, the pharmacokinetics of efgartigimod is well described.

Toxicology was investigated sufficiently in rats, rabbits and cynomolgus monkey. In brief, no safety signal likely to be relevant for translation to human administration was detected and no specific guidance was given in support of clinical studies that would exceed standard monitoring.

CHMP considered that the non-clinical data submitted supports the use of efgartigimod in the approved indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

An overview of the clinical studies submitted are provided in Table 8 and Table 9 for healthy subjects and patients with gMG, respectively.

Table 8 – Overview of PK, PD and immunogenicity assessment in healthy subjects

Study	ARGX-113-1501	ARGX-113-1702
Design	Double-blinded, placebo-controlled	Open-label
Study Population	Healthy subjects	Healthy subjects
Dosage and administration	Efgartigimod IV or matched placebo infused over 2 hours SAD (4 active, 2 placebo subjects per cohort)[a]: Cohort 1: 0.2 mg/kg Cohort 2: 2.0 mg/kg Cohort 3: 10 mg/kg Cohort 4: 25 mg/kg Cohort 5: 50 mg/kg MAD (6 active, 2 placebo subjects per cohort): Cohort 7: 10 mg/kg q4d (6 infusions) Cohort 8: 25 mg/kg q7d (4 infusions)[b] Cohort 9: 10 mg/kg q7d (4 infusions) Cohort 10: 25 mg/kg q7d (4 infusions)	Treatment A (n=8): Single dose of efgartigimod IV 10 mg/kg infused over 2 hours Treatment B (n=8)[c]: Single dose of efgartigimod SC 10 mg/kg Treatment C (n=16)[c]: Efgartigimod IV 20 mg/kg 2-hour infused on day 1 and day 4; followed by efgartigimod SC 300 mg q7d for 8 weeks starting on day 8; stratified based on weight at screening to subsets C1 (n=8; 50-70 kg) or C2 (n=8; 80-100 kg) Treatment D (n=8): Efgartigimod IV 10 mg/kg q7d infused over 1 hour q7d (4 infusions)
PK Assessments (serum/urine)	SAD: Blood samples at predose and at the end of infusion (2 h) up to 28 days postdose; urine collected up to 72 hours postdose MAD: Blood samples at predose and at the end of each infusion (2h), during the dosing interval of 4 or 7 days and up to 28 days after the last infusion	Treatment A: Blood samples at predose and at 1 h, at the end of infusion (2 h) up to 42 days postdose Treatment C: Blood samples at predose and at end of infusion (2 h) on days 1 and 4. Predose on day 8[c] Treatment D: Blood samples at predose and the end of infusion (1 h) on days 1, 8, 15 and 22 and up to 42 days after 4th infusion
PD Assessments (serum)	Total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE and IgM[d] SAD: At predose and at the end of infusion (2 h) up to 28 days postdose MAD: At each infusion at predose and at the end of infusion (2 h) with dense sampling during each dosing interval and up to 56 days after the last infusion	Total IgG, IgG1, IgG2, IgG3, IgG4, IgA and IgM[d] Treatment A: At predose and up to 56 days postdose Treatment C: At predose on days 1, 4 and 8[c] Treatment D: At predose on days 1, 8, 15 and 22 and up to 56 days after 4th infusion

Study	ARGX-113-1501	ARGX-113-1702
Immunogenicity (serum)	SAD: At predose and on day 5 up to 28 days postdose MAD: At predose on days 1, 5, 9, 13, 17 and 21 (for q4d) or on days 1, 8, 15 and 22 (for q7d) and up to 28 days after the last infusion	Treatment A: At predose and on day 8 up to 56 days postdose Treatment C: At predose on days 1 and 8[c] Treatment D: At predose on days 1, 8, 15 and 22 and up to 56 days after 4th infusion

Ig=immunoglobulin; IV=intravenous; MAD=multiple ascending dose; PD=pharmacodynamics; PK=pharmacokinetics; q4d=every four days; q7d=every 7 days; SAD=single ascending dose; SAE=serious adverse event; SC=subcutaneous

[a] No subjects were enrolled in the optional cohort 6.

[b] Dosing in the original 25 mg/kg q7d MAD cohort (cohort 8) was discontinued due to an SAE of hyperventilation that occurred after a subject in this cohort received a single dose of efgartigimod. The event was determined to be unrelated to efgartigimod and a new cohort (cohort 10) was initiated (Module 2.7.4, Table 38).

[c] The PK and PD of efgartigimod after SC administration are not discussed as the SC formulation of efgartigimod is not subject of this application.

[d] Evaluation of IgA, IgD, IgE, or IgM are discussed in Module 2.7.4, Section 3.1.

Table 9 - Overview of PK, PD and immunogenicity assessment in patients with gMG

Study	ARGX-113-1602 (Phase 2)	ARGX-113-1704 (Phase 3)	ARGX-113-1705 (Phase 3)
Design	Double-blinded, placebo-controlled	Double-blinded, placebo-controlled	Open-label extension of ARGX-113-1704
Study Population	Patients with gMG (AChR-Ab seropositive)	Patients with gMG (AChR-Ab seropositive or seronegative)	Patients with gMG (AChR-Ab seropositive or seronegative)
Dosage and administration	Efgartigimod IV 10 mg/kg or matched placebo IV infusions over 2 hours in one treatment cycle of 4 infusions at weekly intervals (q7d for 4 infusions)	Efgartigimod IV 10 mg/kg or matched placebo IV infusions over 1 hour in treatment cycles of 4 infusions at weekly intervals (q7d for 4 infusions) Re-treatment/subsequent cycles of 4 infusions at weekly intervals initiated based on clinical response	Efgartigimod IV 10 mg/kg IV infusions over 1 hour in treatment cycles of 4 infusions at weekly intervals (q7d for 4 infusions) Re-treatment/subsequent cycles of 4 infusions at weekly intervals initiated based on clinical response
PK Assessments (serum)	At predose and within 30 min after the end of infusion on days 1, 8, 15 and 22 and up to 28 days after the 4th infusion[a]	At predose and within 1 hour after the end of infusion on days 1, 8, 15 and 22 and up to 14 days after 4th infusion of each cycle and at EoS/ED[b]	No PK samples taken

Study	ARGX-113-1602 (Phase 2)	ARGX-113-1704 (Phase 3)	ARGX-113-1705 (Phase 3)
PD Assessments (serum)	Total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM and AChR-Ab[c]. At predose on days 1, 8, 15 and 22, and up to 56 days after the 4th infusion[a]	Total IgG, IgG1, IgG2, IgG3, IgG4, AChR-Ab and anti-MuSK antibodies[d] At predose on days 1, 8, 15 and 22 and up to 35 days after the 4th infusion of each cycle, every 2 weeks in the inter treatment cycle period, at each unscheduled visit and at EoS/ED	Total IgG, IgG1, IgG2, IgG3, IgG4, AChR-Ab and anti-MuSK antibodies[d] Part A: At predose on days 1, 8, 15 and 22 and up to 30 days after the 4th infusion of each cycle, every 30 days in the inter treatment cycle period, at each unscheduled visit and at the end-of-part A/ED
Immunogenicity (serum)	At predose and on days 1, 15 and 22 and up to 56 days after 4th infusion	At predose on days 1 and 22 and at 14 and 35 days after 4th infusion of first cycle At predose on day 1 and 35 days after 4th infusion in subsequent cycles, at each unscheduled visit and at EoS/ED	Part A: At predose on days 1 and 22 of each cycle and at the end-of-part A/ED Part B: At predose on day 1 of each cycle and at EoS/ED.

AChR-Ab=anti-acetylcholine receptor antibody; ED=early discontinuation; EoS=end of study; Ig=immunoglobulin; IV=intravenous; gMG=generalized myasthenia gravis; MuSK=muscle-specific kinase; PD=pharmacodynamics; PK=pharmacokinetics; q7d=every 7 days

[a] Optional visits including assessments for PK and PD were scheduled at 4 days after each infusion (ie, on days 5, 12, 19 and 26).

[b] For Japanese patients, in each cycle additional PK samples were taken at 48 and 96 hours after the first and fourth infusion.

[c] Evaluation of IgA, IgD, IgE, or IgM are discussed in Module 2.7.4, Section 3.2.1.

[d] AChR-Ab were measured in AChR-Ab seropositive patients only. Anti-MuSK antibodies were measured in anti-MuSK seropositive patients only.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Efgartigimod alfa is a human recombinant immunoglobulin 1(IgG1)-derived Fc fragment produced by recombinant DNA technology. Efgartigimod alfa is engineered for increased affinity to the neonatal Fc Receptor (FcRn), resulting in the reduction of the levels of circulating IgG including autoantibodies. Efgartigimod alfa has been developed for treatment of adult patients with generalized Myasthenia Gravis (gMG). The molecular weight of efgartigimod alfa is approximately 54 kDa.

The clinical pharmacology program assessed the PK, PD, and immunogenicity of efgartigimod administered via intravenous (IV) infusion in two Phase 1 studies in healthy subjects (ARGX-113-1501 and ARGX-113-1702) and in a Phase 2 and a Phase 3 study in patients with gMG (ARGX-113-1602 and ARGX-113-1704, respectively). The PD and immunogenicity of efgartigimod have also been evaluated in the ongoing open label extension study (ARGX-113-1705) based on data obtained up to the cut-off date of 01 February 2021. Population PK/PD analyses were performed to support the dosing regimen in the phase 3 studies in patients with gMG, and to investigate if intrinsic factors (such as body weight, race, age and gender) affect the PK or PD profile of efgartigimod. The recommended dose is 10 mg/kg as a 1-hour IV infusion administered in cycles of once weekly infusions for 4 weeks.

Dose rationale

The recommended dose regimen of 10 mg/kg every week for 4 weeks cycles has been appropriately justified, based on an analysis of the clinical studies and a PopPK analysis. Overall, in the single ascending dose study, doses from 0.2 - 50 mg/kg were evaluated and in the multiple ascending dose study, 10 and 25 mg/kg were evaluated. The dose of 10 mg/kg is endorsed.

Analytical methods

The assay for determination of efgartigimod in serum and urine was a quantitative enzyme-linked immunosorbent assay (ELISA). The anti-drug antibody (ADA) method was an affinity capture elution (ACE) bridging ELISA. Many of the samples positive for ADAs against efgartigimod came from placebo treated patients or were pre-treatment samples. However, the incidence was comparable between healthy subjects (between 10% and 32.5%) and MG patients (between 15.2% and 29.2%). For determination of immunoglobulins, a quantitative ELISA was used for total IgG and assays similar to that of a sandwich ELISA were used for IgG subtypes. A radioimmunoassay, where AChRs from human muscle are labelled with 125I-α-bungarotoxin were used to determine the binding and blocking AChR-Abs in serum samples. Muscle-specific receptor tyrosine kinase (MuSK) antibodies were determined via a quantitative ELISA.

Population PK modelling

The starting point for the model development was a PK model which was previously developed to describe the PK of efgartigimod in study ARGX-113-1501 in healthy subjects and then further optimised to describe the PK of efgartigimod in MG patients enrolled in the Phase 2 study ARGX-113-1602. This model consisted of a three-compartmental model with linear clearance and included the assumption that the volume of the third (peripheral) compartment (V3) was equal to the volume of the second (peripheral) compartment (V2). Inter-individual variability (IIV) was identified for clearance (CL), the central volume of distribution (V1), the inter-compartmental clearance (Q2), and the volume of the peripheral compartments (V2=V3). Furthermore, covariance for the IIV was estimated for CL, V1, and V2=V3. An additive residual error model was used, which is the standard for log-transformed data. No covariates were included in this model for study ARGX-113-1602. The same random effect structure as identified for healthy subjects was used, as well as the residual error model. The CL was found to be reduced by 12% in MG patients (fCL_{MG}=0.878), as compared to the typical value in healthy subjects (i.e. CL=0.153 L/h).

The PK of efgartigimod in study ARGX-113-1704 could be described by the existing Phase 2 PK structural model. However, due to the limited number of samples in the terminal phase, the IIV on peripheral parameters (i.e. IIV on V2 and IIV on Q2) needed to be removed. A statistically significant covariate effect of body weight on CL and V1 and of eGFR on CL was identified.

Based on the Phase 3 data, a formal covariate analysis was performed to determine if the preselected covariates (age, body weight, BMI, race, ethnicity, gender, estimated glomerular filtration rate (eGFR), albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ADA status, and gMG concomitant medication (i.e., NSIDs only, steroids only, both NSIDSs and steroids, or neither of both)) could explain any observed variability in the PK and/or the total IgG model parameters.

Existing PK/PD model of IgG and AChRAb suppression in MG patients

A schematic representation of the PK/PD model is shown in Figure 5.

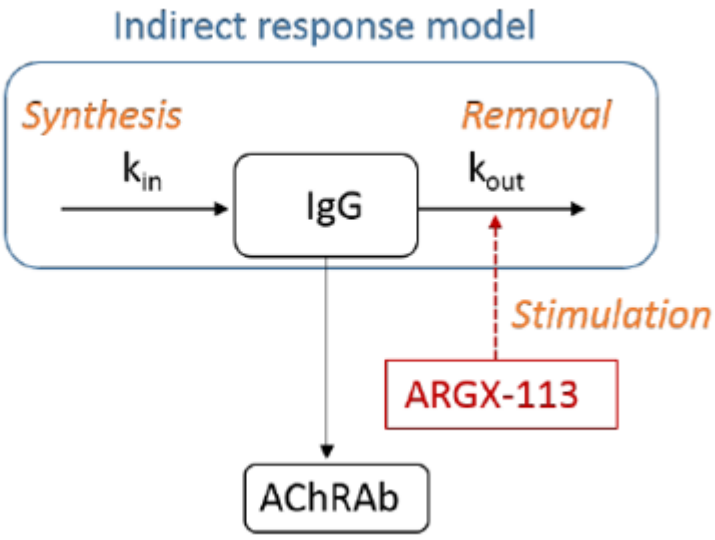


Figure 5 – Schematic representation of the indirect response turnover model, in which efgartigimod stimulates the degradation rate of total IgG. Subsequently, the suppression of total IgG is directly linked to the suppression of the binding AChRAb.

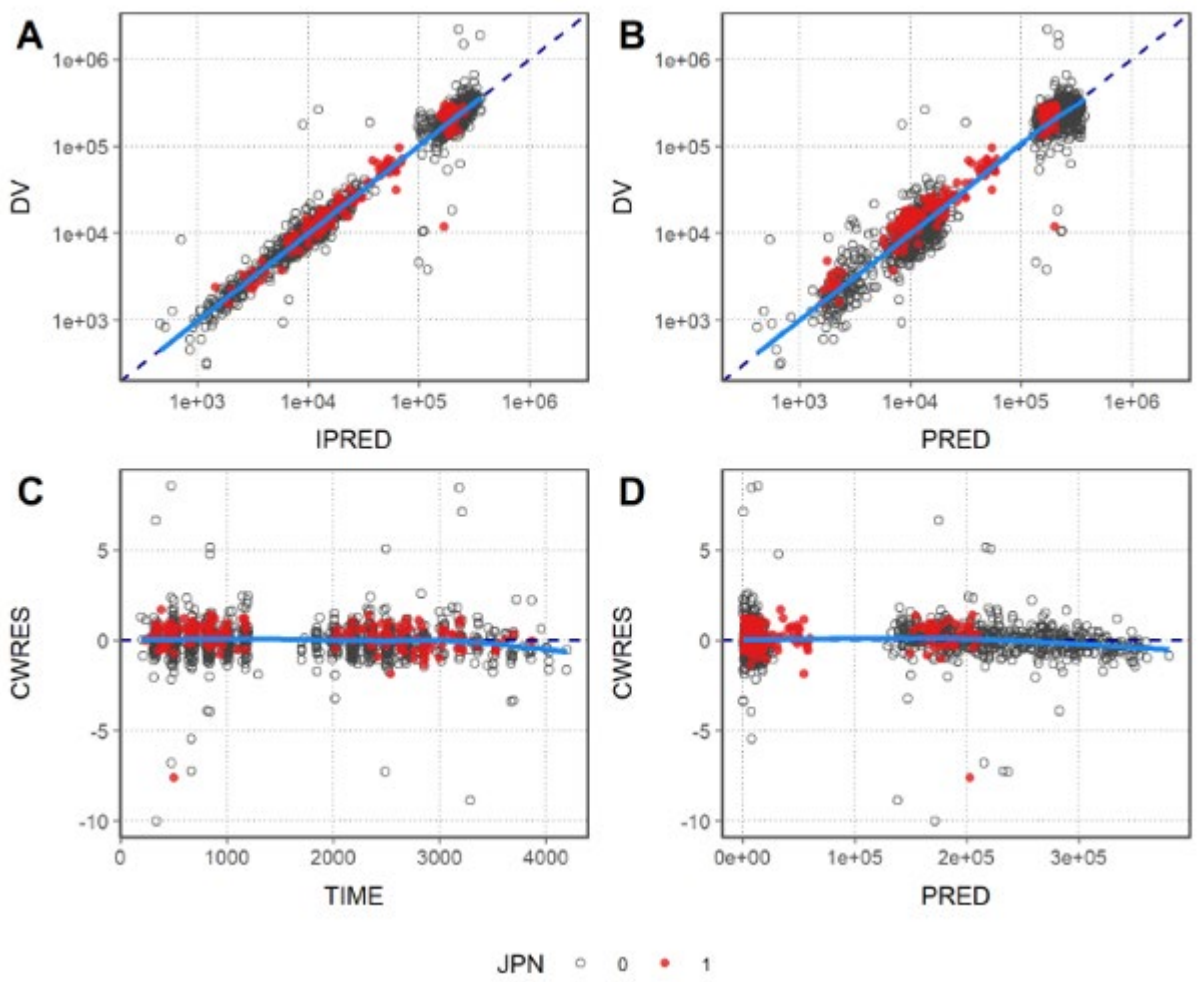
The final parameter estimates were estimated with good precision (all RSE <30%).

Model validation

Model validation (GOF and VPCs) showed good agreement between the observed and predicted data.

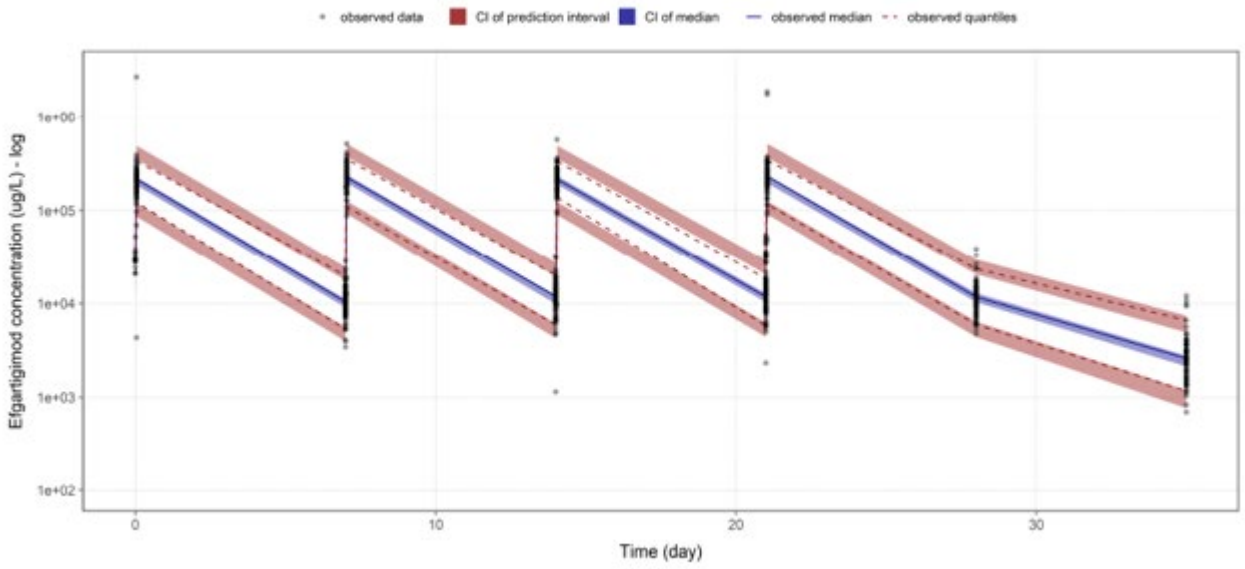
The data management and modelling strategy approach allows to characterize the PK properties of efgartigimod in patients. The developed population PK model incorporates first-order distribution and elimination kinetic processes, which are in accordance with the dose proportionality assessment study. The final population PK incorporates two peripheral distribution compartments.

Model evaluation suggests an adequate description of the PK profile of efgartigimod over time in terms of the typical profile but a slight over-prediction of the inter-individual variability, which may compromise the predicted exposure.



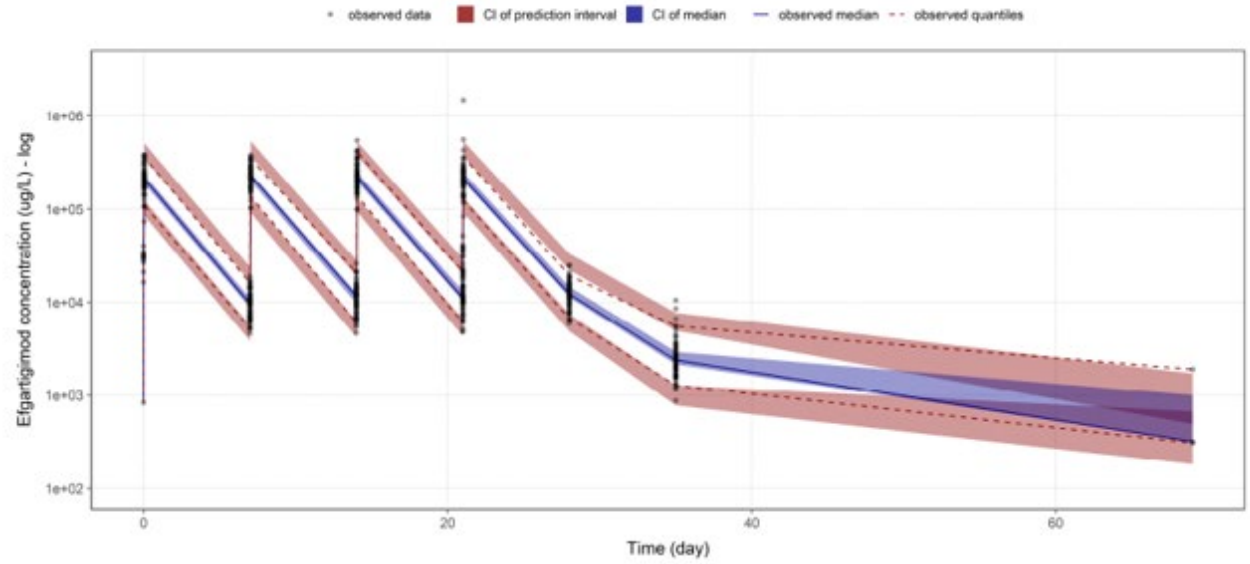
A: Observations (DV) *versus* individual predictions (IPRED). B: Observations (DV) *versus* population predictions (PRED). C: Conditional weighted residual (CWRES) *versus* time (in hours). D: Conditional weighted residuals (CWRES) *versus* population predictions (PRED). Blue line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating 0 (C and D). Red dots: DV and CWRES values for observations from Japanese subjects. Black open circles: DV and CWRES values for observations from non-Japanese subjects.
DV, PRED, and IPRED are plotted in ng/mL.

Figure 6 – Goodness-of-fit plots for the PK model F.PK mod, all cycles



Grey dots: prediction-corrected observations; *blue dashed line*: prediction-corrected observed median; *red dashed lines*: 5th and 95th percentiles observations; *blue area*: 90% confidence interval for the predicted median; *red areas*: 90% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 7 – Prediction-corrected visual predictive checks: PK of efgartigimod in cycle 1 for all patients in ARGX-113-1704, obtained with the PK model F.PK.mod, identified on PK data from ARGX-113-1704.



Grey dots: prediction-corrected observations; *blue dashed line*: prediction-corrected observed median; *red dashed lines*: 5th and 95th percentiles observations; *blue area*: 90% confidence interval for the predicted median; *red areas*: 90% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 8 – Prediction-corrected visual predictive checks: PK of efgartigimod in cycle 2 for all patients in ARGX-113-1704, obtained with the PK model F.PK.mod, identified on PK data from ARGX-113-1704.

Absorption

As efgartigimod is a therapeutic protein, no dedicated absorption, distribution, metabolism and excretion (ADME) study was performed. The product is intended for intravenous administration and accordingly Cmax occurred at the end of infusion.

Reported PK data observed in the target population dosed with the intended 10 mg/kg IV (study 1704) are presented in Table 11. Mean Cmax and Ctrough remained stable after each infusion throughout cycle 1 and cycle 2.

Table 11 – Summary of the efgartigimod pharmacokinetic parameters per cycle

	4 Weekly Infusions of Efgartigimod IV 10 mg/kg (1-h Infusion)			
	Cycle 1			
	1st Infusion (week 0)	2nd Infusion (week 1)	3rd Infusion (week 2)	4th Infusion (week 3)
C_{trough} (µg/mL)	*NA*	13.9 (28.3)$^{n=82}$	12.9 (6.47)$^{n=80}$	12.8 (6.25)$^{n=81}$
C_{max} (µg/mL)	242 (230)$^{n=80}$	235 (73.6)$^{n=81}$	234 (76.2)$^{n=80}$	253 (196)$^{n=80}$
R_{ac}	*NA*	*NA*	*NA*	1.78 (5.39)$^{n=77}$
	Cycle 2			
	1st Infusion (week 0)	2nd Infusion (week 1)	3rd Infusion (week 2)	4th Infusion (week 3)
C_{trough} (µg/mL)	*NA*	10.4 (4.30)$^{n=63}$	12.3 (6.36)$^{n=61}$	12.9 (6.88)$^{n=60}$
C_{max} (µg/mL)	221 (64.6)$^{n=62}$	232 (58.5)$^{n=63}$	242 (91.5)$^{n=61}$	246 (189)$^{n=60}$
R_{ac}	*NA*	*NA*	*NA*	1.20 (1.10)$^{n=59}$
	Cycle 3			
	1st Infusion (week 0)	2nd Infusion (week 1)	3rd Infusion (week 2)	4th Infusion (week 3)
C_{trough} (µg/mL)	*NA*	36.4 (69.9)$^{n=6}$	7.13 (2.91)$^{n=4}$	7.52 (1.25)$^{n=5}$
C_{max} (µg/mL)	226 (21.2)$^{n=7}$	174 (113)$^{n=5}$	145 (19.7)$^{n=5}$	153 (24.5)$^{n=5}$
R_{ac}	*NA*	*NA*	*NA*	0.692 (0.110)$^{n=5}$

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Table 14.2.7.3

C_{max}=maximum observed serum concentration; C_{trough}=serum concentration observed prior to start of infusion at week 1, week 2 and week 3; IV=intravenous; n=number of observations; NA=not assessable; PK=pharmacokinetics; R_{ac}=accumulation ratio based on C_{max}; SD= standard deviation

Note: Values are arithmetic means (SD).

Distribution

Volume of distribution has also been evaluated for gMG patients using the popPK approach. In the final PK model, the estimated patient Vd was approximately 13 L.

Elimination

The terminal half-life (t½) is approximately 3-5 days, and the clearance 0.21 L/h. At the recommended dose of 10 mg/kg, the fraction excreted in urine during 72 hours was 0.1% (n=4).

The primary elimination pathways for mAbs, and expectedly also Fc fragments like efgartigimod, are degradation by the reticuloendothelial system (like endogenous IgG) or by target-mediated elimination

Dose proportionality and time dependencies

Dose proportionality in efgartigimod PK after a single dose of efgartigimod 0.2 to 50 mg/kg IV was assessed in study ARGX-113-1501 by means of a power model on ln-transformed Cmax and AUC0-inf with dose as fixed effect. The point estimates of the slopes with 90% CI are presented in Table 12.

According to the power model, dose proportionality in the dose range of 2.0 – 50 mg/kg has been demonstrated for the exposure parameters Cmax and AUC0-inf.

Table 12 – Dose proportionality of efgartigimod PK as assessed by a power model

Parameter	Dose Range (mg/kg)	Slope Estimate	90% CI	90% CI (reference)
C_{max}	0.2 - 50	1.1306	1.0824-1.1788	0.8745-1.1255
$AUC_{0\text{-}inf}$	2.0 - 50[a]	0.9522	0.8866-1.0178	0.7847-1.2153

Source: Module 5.3.3.1, ARGX-113-1501 CSR, Table 14.2.2.5
$AUC_{0\text{-}inf}$=area under the concentration-time curve from time zero to infinity; CI=confidence interval;
C_{max}=maximum observed concentration
Note: Dose proportionality was assessed by a power model using ln-transformed $AUC_{0\text{-}inf}$ and C_{max}.
[a] $AUC_{0\text{-}inf}$ could not be properly estimated in the 0.2 mg/kg dose group.

During a treatment cycle of 4 weekly infusions of efgartigimod IV 10 mg/kg in patients with gMG, efgartigimod did not accumulate from day 1 to day 22, as evidenced by stable $AUC_{0\text{-}168h}$ and Cmax. The accumulation ratio based on $AUC_{0\text{-}168h}$ was 0.965 (ARGX-113-1602, Table 13).

Table 13 – Summary of efgartigimod PK parameters after 4 weekly infusions of efgartigimod IV 10mg/kg in patients with gMG

	4 Weekly Infusions of Efgartigimod IV 10 mg/kg (2-h Infusion) (N=12)			
	1st Infusion (week 0)	2nd Infusion (week 1)	3rd Infusion (week 2)	4th Infusion (week 3)
C_{trough} (µg/mL)	*NA*	7.82 (2.92)	11.1 (5.37)	11.2 (5.22)
C_{max} (µg/mL)	187 (58.0)	177 (32.2)	157 (33.2)	168 (43.7)
t_{max} (h)	2.44 (2.08-2.58)	2.50 (2.08-2.50)	2.50 (2.07-2.50)	2.46 (2.08-2.67)
$AUC_{0\text{-}168h}$ (µg.h/mL)	8930 (3127)	9036 (2337)	8557 (2558)	8284 (2784)
$t_{1/2}$ (h)	*NA*	*NA*	*NA*	117 (18.8)
R_{ac}	*NA*	*NA*	*NA*	0.965 (0.265)

Source: Module 5.3.5.1, ARGX-113-1602 CSR, Table 14.3.8.2
$AUC_{0\text{-}168h}$=area under the concentration-time curve (AUC) from time zero up to 168h; C_{max}=maximum observed concentration; C_{trough}=serum concentration observed prior to start of infusion; gMG=generalized myasthenia gravis; IV=intravenous; N=number of patients; NA=not assessable; PK=pharmacokinetics; SD=standard deviation; R_{ac}=accumulation ratio based on $AUC_{0\text{-}168h}$; $t_{1/2}$=apparent elimination half-life; t_{max}=time of C_{max}
Note: Values are arithmetic means (SD) except median (min-max) for t_{max}.

Inter-individual variability

Population parameter estimates, including interindividual variability, for the final PK model is shown in the table above. In the popPK analysis, the interindividual variability in CL and volume of distribution (Vd) was low with coefficients of variability of 13% and 23%, respectively.

Pharmacokinetics in target population

PK in the target population is similar to the PK in healthy subjects. Reported exposure PK data observed in the target population dosed with the intended 10 mg/kg IV regimen (**study 1704**) are presented in the table above.

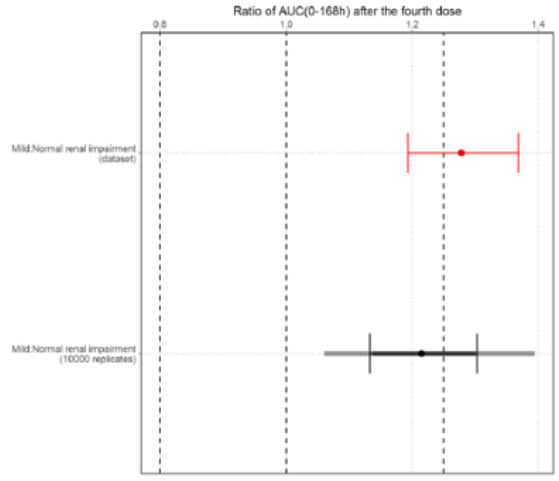
Special populations

Impaired renal function

No dedicated pharmacokinetic studies have been performed in patients with renal impairment. Efgartigimod is considered to be partially filtered by the glomerulus followed by reabsorption and maybe renal degradation.

After 10000 simulated replicates of the popPK dataset, the increase in exposure ($AUC_{0\text{-}168h}$) for patients with mild renal impairment was in the range of 13 to 30%.

Of the 167 patients included in phase 3 studies, 52 and 6 patients were classified as patients with mild (eGFR ≥60 to <90 mL/min/1.73 m2) and moderate (eGFR ≥30 to <60 mL/min/1.73 m2) renal impairment, respectively. No patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) were included.



Source: Module 5.3.3.5, Population PK/PD Report 20 004, Figure 11
$AUC_{0\text{-}168h}$=area under the concentration-time curve from time zero up to 168h; CI=confidence interval; IIV=interindividual variability
Note: Fold change in $AUC_{0\text{-}168h}$ after the fourth dose, assuming body weight dependent dosing. Red bar: ratio of $AUC_{0\text{-}168h}$ after the fourth weekly infusion based on the original data from ARGX-113-1704. Red dot: median of $AUC_{0\text{-}168h}$ ratio based on the dataset. Interval between the vertical connected solid red lines: 90% CI of the $AUC_{0\text{-}168h}$ ratio. Black bar: ratio of $AUC_{0\text{-}168h}$ after the fourth infusion based on 10 000 simulations of the dataset. Black dot: median of $AUC_{0\text{-}168h}$ ratio based on the 10 000 replicates of the dataset. Interval between the vertical connected solid black lines: 90% CI of the $AUC_{0\text{-}168h}$ ratio based on the 10 000 replicates of the dataset. Grey areas: 5th and 95th percentiles of the 10 000 ratios and their 90% CI based on parameter uncertainty and IIV. Vertical dashed lines: reference lines (0.8, 1, 1.25).

Figure 9 – Forest plot evaluating the effect of mild renal impairment on $AUC_{0\text{-}168h}$

Impaired hepatic function

No dedicated pharmacokinetic study has been performed in patients with hepatic impairment, and no patients with hepatic impairment was included in the clinical studies. In the popPK analysis, hepatic function markers (albumin, total bilirubin, AST, ALP and ALT) did not affect the PK of efgartigimod.

Gender

According to the PopPK model, gender does not seem to affect the PK of efgartigimod.

Weight

PopPK simulations with the chosen body weight adjusted dose regimen suggest an impact of high body weight on exposure. Following weekly doses of 1200 mg (corresponding to a patient weight of 120 kg), the median increase in exposure ($AUC_{0\text{-}168h}$) was 36%, compared to the reference subject with a median weight of 79 kg. Subjects with low body weight (here simulated for the 5th percentile body weight of 53 kg) have a median exposure of 80% of the reference patient. These deviations in exposure due to body weight are considered low and insignificant. Baseline body weight in the phase 3 study 1704 in patients on efgartigimod alfa ranged from 49 to 229 kg, which is considered a satisfactorily wide weight range.

Age

Age does not seem to affect the PK of efgartigimod. The effect of age on efgartigimod PK was assessed in the popPK analysis, and age was not found to influence any of the model parameters of the final model. Table 14 below shows the distribution of age in the elderly population.

Table 14 – Overview of the elderly population with available pharmacokinetic data included in the clinical development program of efgartigimod IV

Healthy subjects			
ARGX-113-1501	(0/44)	(0/44)	(0/44)
ARGX-113-1702	(0/32)	(0/32)	(0/32)
Patients with gMG			
ARGX-113-1602	(3/12)	(1/12)	(0/12)
ARGX-113-1704	(9/84)	(2/84)	(0/84)
Overall	**(12/172)**	**(3/172)**	**(0/172)**

Source: Module 5.3.3.1, ARGX-113-1501 CSR Listing 16.2.2.1, Module 5.3.3.1, ARGX-113-1702 CSR, Listing 16.2.4.1, Module 5.3.5.1, ARGX-113-1602 CSR, Listing 16.2.4.1, Module 5.3.5.1, ARGX-113-1704 CSR, Listing 16.2.4.2, Module 5.3.5.4
Note: Number of subjects receiving at least 1 dose of efgartigimod IV.

Race

According to the PopPK model, race does not seem to affect the PK of efgartigimod. The most common race category was white (82.1%), followed by Asian (10.7%), and Black or African American (3.6%).

Pharmacokinetic interaction studies

No clinical DDI studies have been conducted.

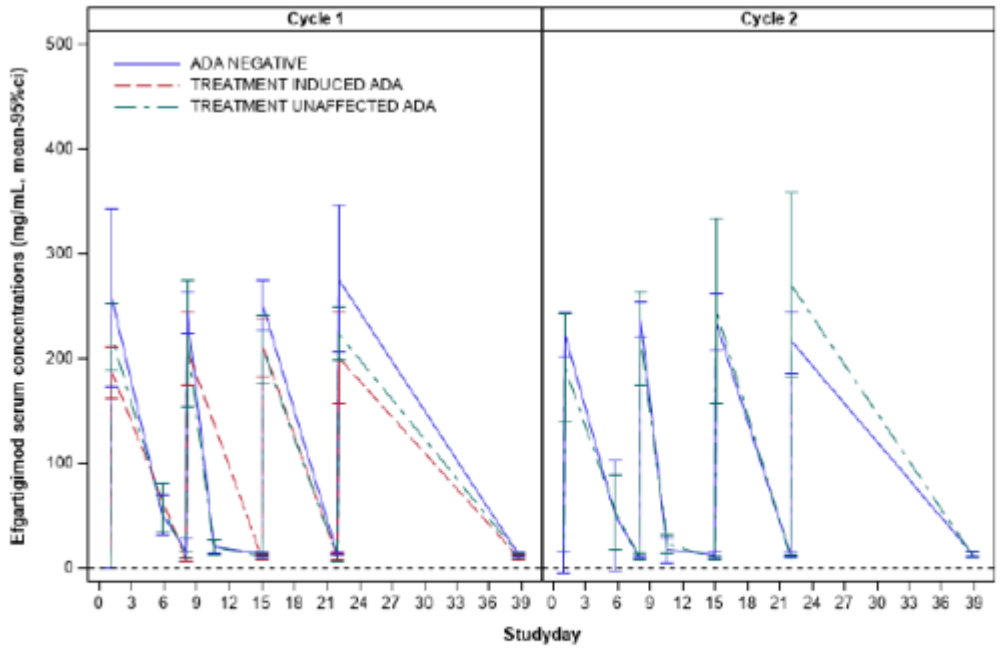
Immunogenicity

In study 1704, the prevalence of ADA positive patients at baseline was similar in the treatment and the placebo groups, and no treatment-boosted ADAs was observed. The incidence of treatment-induced ADAs was 20.5% (n=17) in the treatment group compared to 7.3% (N=6) in the placebo group. As for neutralising antibodies (NAbs), one patient in each group was positive at baseline. The incidence of treatment-induced NAbs was 7.2% (n=6) in the treatment group and 3.7% (n=3) in the placebo group.

The baseline positive ADAs and treatment-induced ADAs in the placebo group are considered to be pre-existing cross-reacting antibodies or false-positive ADA results.

There was no indication of a clinically relevant impact of pre-existing antibodies, treatment-induced/boosted ADA and NAb on PK.

Figure 10 – Efgartigimod serum concentrations by ADA subject classification by cycle in ARGX-113-1704 study



Patients with treatment-induced ADA are not shown for cycle 2 due to the low number of patients (n=4). In cycle 2, nine patients were classified as treatment unaffected and 50 as ADA negative.
Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 14, Table 14.2.7.5.

AChR-Ab Seronegative versus AChR-Ab Seropositive

In study 1704, a total of 38 included patients were AChR-Ab seronegative. Of these 38 patients, 18 had evaluable PK data in cycle 1 and only 12 in cycle 2.

Exposure to efgartigimod in AChR-Ab seronegative patients was higher compared to AChR-Ab seropositive patients, which is considered to be a result of an imbalance of patients with impaired renal function.

Table 15 - Summary of the Efgartigimod Pharmacokinetic Parameters by AChR-Ab Status per Cycle (PK Analysis Set)

Cycle	Parameter	Statistic	AChR-Ab Seronegative				AChR-Ab Seropositive			
			First Infusion (Week 0)	Second Infusion (Week 1)	Third Infusion (Week 2)	Fourth Infusion (Week 3)	First Infusion (Week 0)	Second Infusion (Week 1)	Third Infusion (Week 2)	Fourth Infusion (Week 3)
1	C_{trough} (µg/mL)	n		18	18	18		64	62	63
		mean (SD)	NA	12.5 (4.59)	14.8 (7.66)	14.7 (7.73)	NA	14.3 (32.0)	12.3 (6.04)	12.3 (5.72)
	C_{max} (µg/mL)	n	18	19	18	18	62	62	62	62
		mean (SD)	240 (69.5)	260 (86.8)	253 (61.8)	268 (55.7)	243 (260)	228 (68.1)	229 (79.5)	248 (221)
	R_{ac}	n				18				59
		mean (SD)	NA	NA	NA	1.18 (0.318)	NA	NA	NA	1.96 (6.15)
2	C_{trough} (µg/mL)	n		12	12	12		51	49	48
		mean (SD)	NA	13.6 (5.30)	14.9 (8.03)	15.1 (7.49)	NA	9.65 (3.70)	11.7 (5.81)	12.3 (6.69)
	C_{max} (µg/mL)	n	12	12	12	12	50	51	49	48
		mean (SD)	266 (66.6)	273 (64.1)	352 (109)	308 (137)	210 (59.8)	222 (53.2)	215 (62.9)	231 (198)
	R_{ac}	n				12				47
		mean (SD)	NA	NA	NA	1.22 (0.638)	NA	NA	NA	1.20 (1.19)

Source: Section 14, Table 14.2.7.4

C_{max}=maximum observed serum concentration; C_{trough}=serum concentration observed before the start of infusion at week 1, week 2, and week 3; NA=not assessable; n=number of patients for whom the observation was reported; PK=pharmacokinetics; R_{ac}=accumulation ratio based on C_{max}; SD= standard deviation

2.6.2.2. Pharmacodynamics

Total IgG, IgG subtypes 1 to 4, IgA, IgD, IgE, IgM, anti-acetylcholine receptor antibodies (AChR-Ab) and antimuscle-specific receptor tyrosine kinase (MuSK) antibodies were used as pharmacodynamic markers. Total IgG as well as its IgG subtypes (IgG1, IgG2, IgG3 and IgG4) were evaluated in all clinical studies. Besides, to assess the selective reduction of IgG by efgartigimod, in some studies the level of other isotypes IgA, IgD, IgE and IgM were also determined. In patients with gMG, autoantibodies (AChR-Ab and anti-MuSK antibodies) were determined.

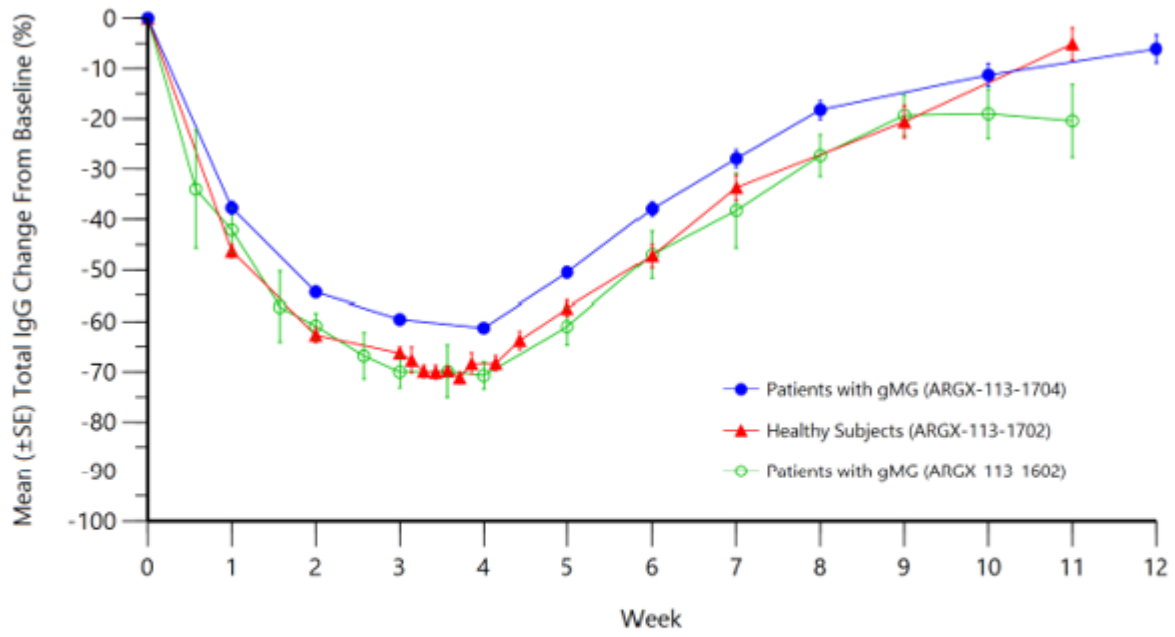
Mechanism of action

The neonatal Fc receptor (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.

Primary and Secondary pharmacology

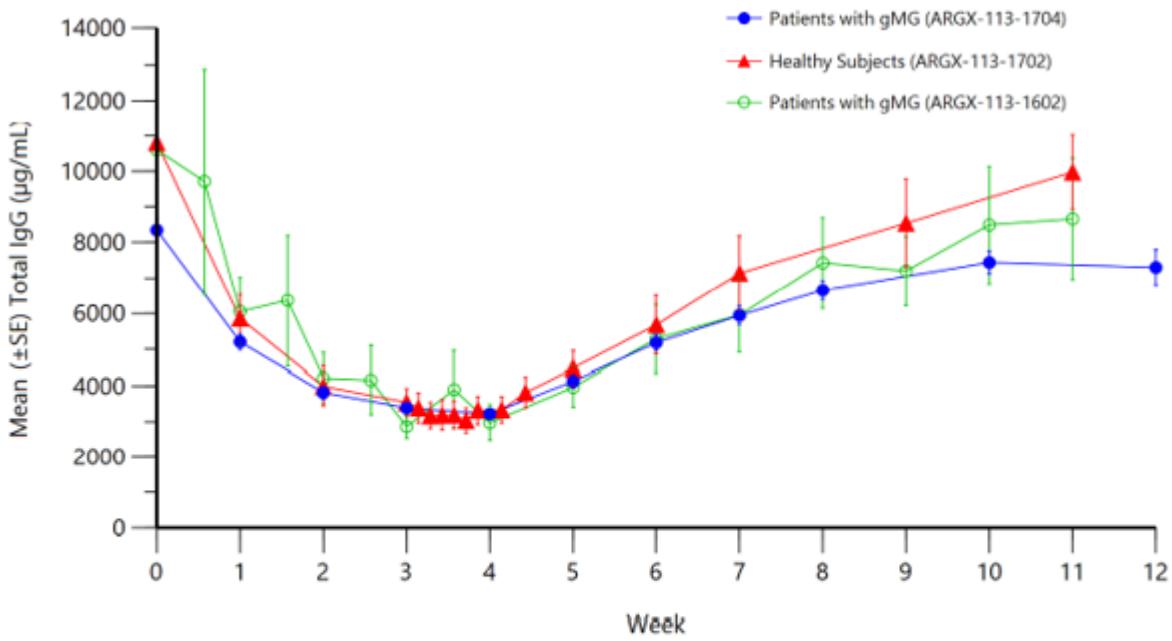
The pharmacodynamic effects elicited by efgartigimod were highly comparable in patients with gMG compared to healthy subjects. After administration of 4 weekly infusions of efgartigimod IV 10 mg/kg, the pattern of total IgG reduction was similar in both populations achieving a maximum reduction one week after the last infusion. Based on the change from baseline values, after 4 weekly infusions of efgartigimod IV 10 mg/kg total IgG was reduced by approximately 70% in healthy subjects and was reduced by 60% to 70% in patients with gMG (Figure 11).

The total IgG baseline values differed in patients with gMG and in healthy subjects. However, at maximum reduction, the absolute total IgG levels were comparable in the two populations (Figure 12). Overall, efgartigimod IV 10 mg/kg in a cycle of 4 weekly infusions consistently reduced total IgG to a nadir level of 2500 to 3500 µg/mL. Similar results as compared to total IgG were observed for the IgG subtypes.



Source: Module 5.3.3., ARGX-113-1702 CSR, Table 14-5, Module 5.3.5.1, ARGX-113-1602 CSR, Table 14.3.6.1 and Module 5.3.5.1, ARGX-113-1704 CSR, Table 14.2.8.1.1
gMG=generalized myasthenia gravis; Ig=immunoglobulin; IV=intravenous; n=number of observations; SD=standard deviation, SE=standard error derived as $SD/\sqrt{n}$
Note: Doses were administered at week 0, week 1, week 2 and week 3.
For total IgG data in healthy subjects, study ARGX-113-1702 was selected as total IgG sampling occurred up to return to baseline levels.

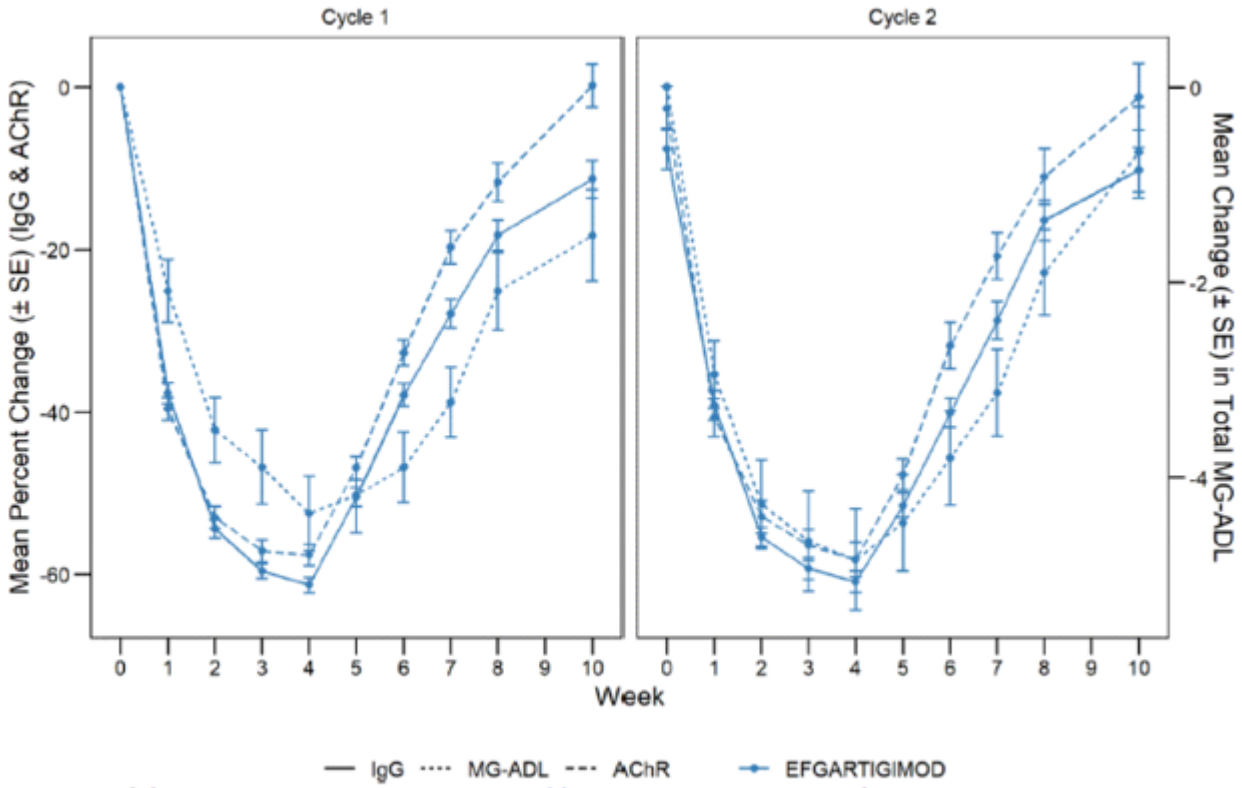
Figure 11 – Mean percent change from baseline in total IgG after 4 weekly infusions of efgartigimod IV 10mg/kg in healthy subjects and patients with gMG



Source: Module 5.3.3.1, ARGX-113-1702 CSR, Table 14-5, Module 5.3.5.1, ARGX-113-1602 CSR, Table 14.3.6.1 and Module 5.3.5.1, ARGX-113-1704 CSR, Table 14.2.8.1.1
gMG=generalized myasthenia gravis; Ig=immunoglobulin; IV=intravenous; n=number of observations; SD=standard deviation, SE=standard error derived as $SD/\sqrt{n}$
Note: Doses were administered at week 0, week 1, week 2 and week 3.
For total IgG data in healthy subjects, study ARGX-113-1702 was selected as total IgG sampling occurred up to return to baseline levels.

Figure 12 – Mean levels of total IgG after 4 weekly infusions of efgartigimod IV 10mg/kg in healthy subjects and patients with gMG

The reduction of AChR-Ab clearly followed the pattern of reduction of total IgG. In addition, the reduction in MG-ADL scores matched the time course of reduced total IgG and AChR-Ab levels (Figure 13). The time course and magnitude in reduction of the pharmacodynamic markers in subsequent cycles was comparable to cycle 1.



Source: Module 5.3.5.1, ARGX-113-1704 CSR, Tables 14.2.1.9.1, 14.2.8.2.1 and 14.2.8.9.2
AChR-Ab=anti-acetylcholine receptor antibody; Ig=immunoglobulin; MG-ADL=Myasthenia Gravis Activities of Daily Living; SE=standard error

Figure 13 – Change in MG-ADL total score and percent change in levels of total IgG and AChR-Ab by cycle in AChR-Ab seropositive population

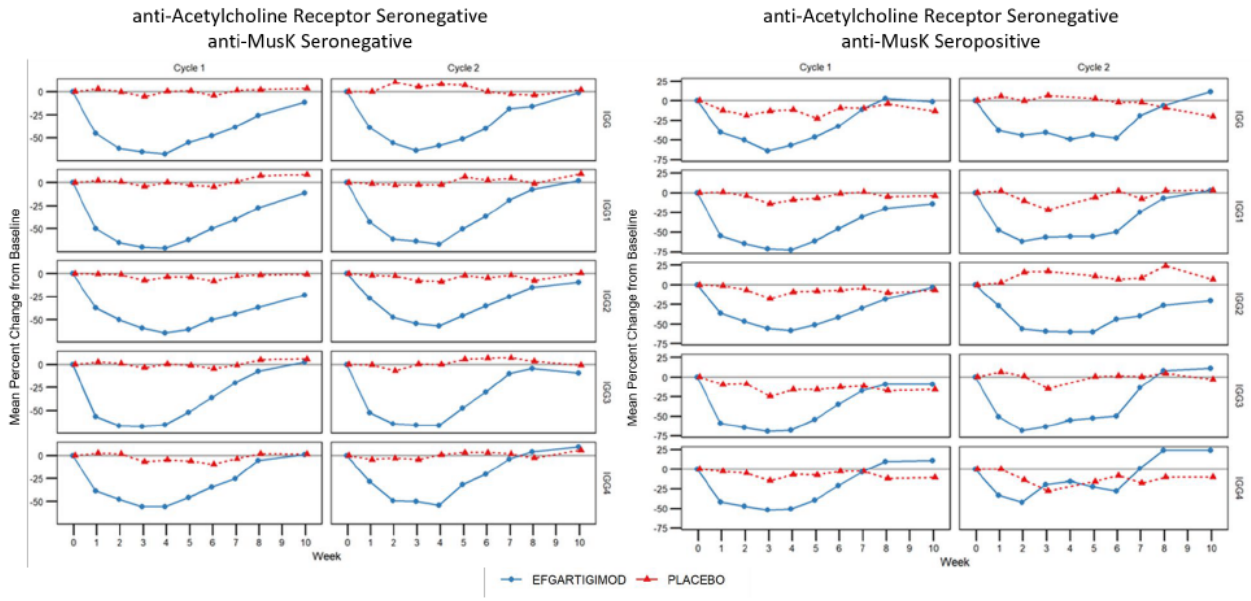
IgG subtypes

Across studies, similar results were obtained for the different IgG subtypes, although the mean reduction in IgG4 was slightly less. In study ARGX-113-1704, the mean IgG4 levels were variable during a cycle, however highly affected by a few outliers. Looking at median and quartile values, as for IgG1, IgG2 and IgG3, the time course of IgG4 reductions was similar to total IgG.

AChR-Ab Serotype

In a pooled PD analysis evaluating the total IgG levels in patients with gMG, the percentage change from cycle baseline did not differ across the first 7 cycles with mean (SE) reductions at week 3 ranging between 53.0 (3.01)% to 62.4 (1.48)% and 55.2 (1.22)% to 59.9 (0.81)% in AChR-Ab seronegative and AChR-Ab seropositive patients, respectively.

The mean percent changes from baseline in levels of total IgG and IgG subtypes in AChR-Ab seronegative patients in study ARGX-113-1704 are shown in Figure 14.



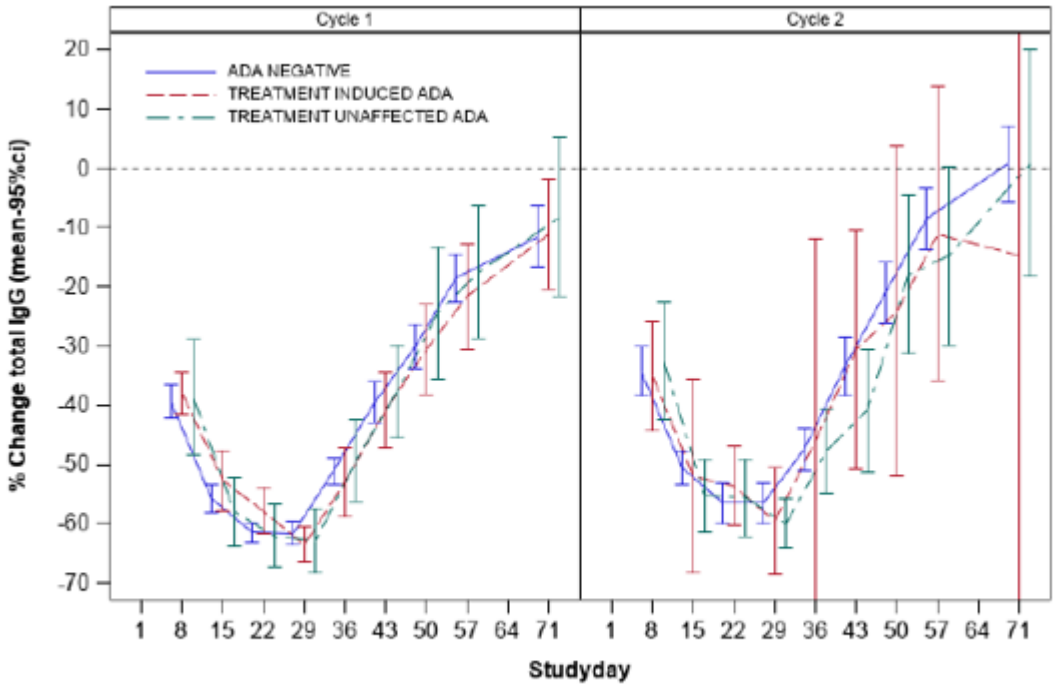
Source: ARGX-113-1704 t_6.1_t_act_cfb_subgrp and t_6.2_t_act_cfb_subgrp
AChR-Ab=anti-acetylcholine receptor antibody; IgG=immunoglobulin G; MuSK=muscle-specific kinase

Figure 14 - Mean Percent Change From Baseline in Levels of Total IgG and IgG Subtypes in AChR-Ab Seronegative Patients – Study ARGX-113-1704

Whereas Anti-AchR antibodies are primarily of the IgG1 and IgG3 isotypes, MuSK Abs are predominantly of the IgG4 isotype. Anti-Lrp4 (low-density lipoprotein-related receptor protein 4) is predominantly of the IgG1 isotype.

Impact of ADA on PD

No difference in the percent change from cycle baseline in total IgG levels (PD) was observed between ADA-negative patients when compared to patients with treatment-induced ADA or treatment-unaffected ADA of the overall population during cycles 1 and 2 (see Figure 15).



Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 14, Table 14.2.8.7.2.

Figure 15 – Mean percent change from cycle baseline in total IgG levels by ADA patient classification by cycle (study ARGX-113-1704)

Secondary pharmacology

By blocking the FcRn receptor, an effect on the levels of albumin could be anticipated. However, no reduction in levels of serum albumin with the administration of efgartigimod was observed.

Due to the pharmacodynamic effects of efgartigimod, no QTc study has been conducted. This is considered acceptable by CHMP. Efgartigimod impact on ECGs is assessed in the safety section of this report.

Relationship between plasma concentration and effect

The exposure parameters Cmax and $AUC_{0\text{-}168h}$ stratified by exposure quartiles for the Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) responder rate in cycle 1 for the AChR-Ab seropositive and overall population is presented in Table 16. The exposure-efficacy analyses indicate that no difference is observed for both MG-ADL and QMG responder rates across quartiles of exposures as measured by the C_{max} and $AUC_{0\text{-}168h}$ after the 4th administration of efgartigimod IV 10 mg/kg in cycle 1 of study ARGX-113-1704.

Table 16 – MG-ADL and QMG response rate stratified by C_{max} and $AUC_{0\text{-}168h}$ quartiles in cycle 1 of study ARGX-113-1704

AChR-Ab Status	Quartile	MG-ADL Responder Rate in Cycle 1				QMG Responder Rate in Cycle 1			
		C_{max} Quartiles[a]		AUC_{0-168h} Quartiles[b]		C_{max} Quartiles[a]		AUC_{0-168h} Quartiles[b]	
Positive	Q1	11/16	(68.8%)	14/17	(82.4%)	10/16	(62.5%)	11/17	(64.7%)
	Q2	8/15	(53.3%)	8/16	(50.0%)	9/15	(60.0%)	10/16	(62.5%)
	Q3	12/16	(75.0%)	11/16	(68.8%)	11/16	(68.8%)	9/16	(56.3%)
	Q4	11/15	(73.3%)	11/16	(68.8%)	9/15	(60.0%)	11/16	(68.8%)
All	Q1	15/20	(75.0%)	16/21	(76.2%)	12/20	(60.0%)	13/21	(61.9%)
	Q2	8/20	(40.0%)	11/21	(52.4%)	13/20	(65.0%)	13/21	(61.9%)
	Q3	16/20	(80.0%)	16/21	(76.2%)	11/20	(55.0%)	11/21	(52.4%)
	Q4	16/20	(80.0%)	14/20	(70.0%)	13/20	(65.0%)	14/20	(70.0%)

Source: ARGX-113-1704 - EMA Questions, Table 49.1.1.1 to 49.1.4.2

AChR-Ab=anti-acetylcholine receptor antibody; AUC_{0-168h}=area under the concentration-time curve from time zero up to 168h; C_{max}=maximum observed concentration; Q=quartile; MG-ADL=Myasthenia Gravis Activities of Daily Living; QMG=Quantitative Myasthenia Gravis

Note: MG-ADL Responder=a reduction of at least 2 points on the MG-ADL total score that was sustained for at least 4 consecutive weeks with the first reduction occurring no later than 1 week after the last infusion.
QMG Responder=a reduction of at least 3 points on the total QMG score that was sustained for at least 4 consecutive weeks with the first of these reduction occurring no later than 1 week after the last infusion.

[a] Quartile cut-off values (25th, 50th and 75th percentile) for C_{max} were 184, 219 and 244 µg/mL and 195, 228 and 265 µg/mL in AChR-Ab seropositive and overall population, respectively.

[b] Quartile cut-off values (25th, 50th and 75th percentile) for AUC_{0-168h} were 5997, 6889 and 8638 µg.h/mL and 6011, 7169 and 8863 µg.h/mL in AChR-Ab seropositive and overall population, respectively.

In a similar evaluation, the exposure parameters Cmax and AUC_{0-168h} stratified by exposure quartiles for the adverse events across all cycles in study ARGX-113-1704 are presented in Table 17 and Table 18, respectively. The exposure-safety analyses did not reveal a trend in increasing treatment-emergent adverse events (TEAE)s with higher exposure of efgartigimod.

Table 17 – Overview of Adverse Events by C_{max} quartiles of study ARGX-113-1704

	Q1			Q2			Q3			Q4		
Total number of patients with:	n	%	m	n	%	m	n	%	m	n	%	m
At least 1 TEAE	14	70.0	65	14	70.0	57	17	85.0	51	16	80.0	69
At least 1 serious TEAE	2	10.0	2	0			0			1	5.0	1
At least 1 grade ≥3 TEAE	3	15.0	3	2	10.0	3	1	5.0	1	2	10.0	2
At least 1 TEAE of special interest	8	40.0	13	6	30.0	6	10	50.0	16	13	65.0	19
At least 1 IRR event	1	5.0	1	0			1	5.0	1	1	5.0	1
At least 1 fatal TEAE	0			0			0			0		
At least 1 treatment-related TEAE according to PI	6	30.0	18	6	30.0	16	7	35.0	16	6	30.0	13
At least 1 procedure-related TEAE	0			1	5.0	1	0			0		
At least 1 serious treatment-related TEAE	1	5	1	0			0			0		
At least 1 TEAE for which study drug was discontinued	2	10.0	2	0			0			0		

Source: ARGX-113-1704 - EMA Questions, Table 49.2.1

C_{max}=maximum observed concentration; IRR=infusion-related reaction; n=number of patients with event; m=number of events; PI=principal investigator; Q=quartile; TEAE=treatment-emergent adverse event.

Note: Quartile cut-off values (25th, 50th and 75th percentile) for C_{max} were 195, 228 and 265 µg/mL (based on C_{max} after 4th administration in Cycle 1).
The denominator for the percentage calculations is N: the total number of patients in the safety analysis set per treatment and per quartile group.
Treatment-related is defined as at least possibly drug related according to the investigator, or a missing drug relatedness.

Table 18 – Overview of adverse events by AUC_{0-168h} quartiles in study ARGX-113-1704.

	Q1			Q2			Q3			Q4		
Total number of patients with:	**n**	**%**	**m**	**n**	**%**	**m**	**n**	**%**	**m**	**n**	**%**	**m**
At least 1 TEAE	14	66.7	59	13	61.9	47	21	100	75	16	80.0	66
At least 1 serious TEAE	0			1	4.8	1	1	4.8	1	1	5.0	1
At least 1 grade ≥3 TEAE	0			3	14.3	4	3	14.3	3	2	10.0	2
At least 1 TEAE of special interest	8	38.1	11	7	33.3	11	13	61.9	20	11	55.0	14
At least 1 IRR event	1	4.8	1	0			1	4.8	1	1	5	1
At least 1 fatal TEAE	0			0			0			0		
At least 1 treatment-related TEAE according to PI	5	23.8	16	6	28.6	12	8	38.1	18	7	35.0	18
Ate least 1 procedure-related TEAE	0			1	4.8	1	0			0		
At least 1 serious treatment-related TEAE	0			1	4.8	1	0			0		
At least 1 TEAE for which study drug was discontinued	0			1	4.8	1	0			1	5.0	1

Source: ARGX-113-1704 - EMA Questions, Table 49.2.2

$AUC_{0\text{-}168h}$=area under the concentration-time curve from time zero up to 168h; IRR=infusion-related reaction; n=number of patients with event; m=number of events; PI=principal investigator; Q=quartile; TEAE=treatment-emergent adverse event.

Note: Quartile cut-off values (25th, 50th and 75th percentile) for $AUC_{0\text{-}168h}$ were 6011, 7170 and 8863 µg.h/mL (based on $AUC_{0\text{-}168h}$ after 4th administration in Cycle 1).
The denominator for the percentage calculations is N: the total number of patients in the safety analysis set per treatment and per quartile group.
Treatment-related is defined as at least possibly drug related according to the investigator, or a missing drug relatedness.

2.6.3. Discussion on clinical pharmacology

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 neonatal Fc Receptor (FcRn), resulting in the reduction of the levels of circulating IgG including autoantibodies. Efgartigimod alfa has been developed for treatment of adult patients with generalized Myasthenia Gravis (gMG). The molecular weight of efgartigimod alfa is approximately 54 kDa.

The clinical pharmacology program assessed the PK, PD, and immunogenicity of efgartigimod administered via intravenous (IV) infusion in two phase 1 studies in healthy subjects (ARGX-113-1501 and ARGX-113-1702) and in a Phase 2 and a Phase 3 study in patients with gMG (ARGX-113-1602 and ARGX-113-1704, respectively). In addition, population PK/PD analyses have been performed.

The Phase 2 population PK model consisted of a three-compartmental model with linear clearance. The population PK of efgartigimod in study ARGX-113-1704 could be described by the existing Phase 2 PK structural model. A statistically significant covariate effect of body weight on CL and V1 and of eGFR on CL was identified.

Due to the characteristics of the product (a therapeutic protein), no dedicated absorption, distribution, metabolism and excretion (ADME) study was performed, the effect of renal or hepatic impairment was not formally tested in dedicated clinical trials, and no clinical interaction studies have been undertaken. This is considered acceptable by CHMP since protein products are eliminated by the reticuloendothelial system (like endogenous IgG) or by target-mediated elimination.

In the popPK analysis, hepatic function markers (albumin, total bilirubin, AST, ALP and ALT) did not affect the PK of efgartigimod and as such it is considered that no dose adjustment is required in patients with hepatic impairment. This is appropriately reflected in section 4.2 of the SmPC.

No dose adjustment is required in patients with mild renal impairment. There is insufficient data on the impact of moderate renal impairment and no data on the impact of severe renal impairment on efgartigimod alfa PK parameters (reflected in section 4.2 and 5.2 of the SmPC).

The recommended dose regimen of efgartigimod is 4 weekly infusions of 10 mg/kg IV followed by a treatment pause of individual length. In the clinical development program, the earliest time to re-treatment was 7 weeks from the initial infusion of the previous cycle.

The product is intended for intravenous administration, the bioavailability is therefore 100% and Cmax is reached at the end of infusion. After four infusions, both Ctrough and Cmax values are comparable between healthy subjects and patients. Overall volume of distribution is reported to be 15 to 20 L in the

SmPC, slightly more than that of monoclonal antibodies reflecting the difference in size. The reported values of clearance and half-life (terminal) were approximately 0.1 L/h and 80 to 120 hours, respectively. In patient Study 1602, no accumulation was observed during 4 weekly infusions of efgartigimod 10 mg/kg. In study 1704, the cycle 1 geometric mean accumulation ratio was 1.12.

At the recommended dose of 10 mg/kg, the fraction excreted in urine during 72 hours was 0.1% (n=4). Efgartigimod is not subject to CYP450 metabolism. The primary elimination pathway is expected to be degradation by the reticuloendothelial system or target-mediated elimination (like endogenous IgG). Metabolites are amino acids and small peptides that are recycled into the protein metabolism.

Dose proportionality in the dose range of 2.0–50 mg/kg has been demonstrated for the exposure parameters.

PK in the target population is similar to the PK in healthy subjects. In the popPK analysis, the interindividual variability in CL and volume of distribution (Vd) was low with coefficients of variability of 13% and 23%, respectively. In healthy subjects, Cmax and AUC interindividual variability (CV%) was up to 28% after multiple doses of efgartigimod.

The clinical pharmacology programme in special populations is typical for a protein drug being administered intravenously. Based on popPK analyses, age, gender, race, and body weight do not seem to affect the PK of efgartigimod in a clinically meaningful way. Baseline body weight in the Phase 3 study 1704 in patients on efgartigimod alfa ranged from 49 to 229 kg, which is considered a satisfactorily wide weight range.

No clinical DDI studies have been conducted, which is acceptable. Being a therapeutic protein with no expected cytochrome P450 or transporter involvement, the potential risk of PK interactions between efgartigimod and other drugs is low.

In mice, concomitant administration of efgartigimod and intravenous immunoglobulins (IVIg) affected the exposure of IVIg. Efgartigimod may potentially affect the PK and/or PD of compounds that bind to the human FcRn, i.e, immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass. In clinical studies, efgartigimod did not affect levels of albumin, IgA, IgD, IgE or IgM. Therefore, efgartigimod is not expected to alter the PK and/or PD of medicinal products containing (or derivatives of) albumin or Igs other than IgG.

PopPK analyses found no sign of interaction between efgartigimod and the gMG SoC treatments acetylcholinesterase inhibitors, steroids, and NSIDS. However, currently, there is no clinical experience with concomitant treatment with efgartigimod and immunoglobulins or monoclonal antibodies and concomitant use of efgartigimod and immunoglobulins or monoclonal antibodies should be avoided. This information is appropriately reflected in section 4.5 of the SmPC.

The available data did not show an impact of pre-existing antibodies, treatment-induced/boosted ADA and NAb on PK.

In study 1704, a total of 38 included patients were AChR-Ab seronegative. Of these 38 patients, 18 had evaluable PK data in cycle 1 and only 12 in cycle 2.

Exposure to efgartigimod in AChR-Ab seronegative patients was higher compared to AChR-Ab seropositive patients, which is considered to be a result of an imbalance of patients with impaired renal function.

The primary pharmacodynamic endpoints were reduction in mean total IgG and its subtypes after single and multiple IV infusions of efgartigimod. After administration of 4 weekly infusions of efgartigimod, the pharmacodynamic effects are comparable in patients with gMG compared to healthy subjects, both in

terms of absolute total IgG reduction and percent change from baseline total IgG. Similar results were obtained for the different IgG subtypes.

The timeframe by when normalisation of the total IgG baseline level is expected is reflected in section 5.1 of the SmPC. In the AChR-Ab seropositive population, a clear correlation between MG-ADL score and levels of total IgG and AChR-Ab have been shown.

There was no apparent impact of pre-existing antibodies, treatment-induced/boosted ADA and NAb on efgartigimod PD effects.

By blocking the FcRn receptor, an effect on the levels of albumin could be anticipated. However, no reduction in levels of serum albumin with the administration of efgartigimod was observed.

Due to the pharmacodynamic effects of efgartigimod, no QTc study has been conducted which is considered acceptable by CHMP. Efgartigimod impact on ECGs is assessed in the safety section of this report.

No sign of an exposure-response relationship was found in the exposure-efficacy and exposure-safety analyses with the exposure parameters stratified by exposure quartiles.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of efgartigimod alfa has been studied in two Phase 1 studies in healthy subjects and in a Phase 2 and a Phase 3 study in patients with gMG. 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 is deemed appropriate.

CHMP considered that the clinical pharmacology data submitted supports the use of efgartigimod in the approved indication.

2.6.5. Clinical efficacy

The efficacy of efgartigimod in the applied indication (treatment of generalized Myasthenia Gravis) has been evaluated in 3 clinical studies (Table 19):

- A phase 2, double-blinded, placebo-controlled study ARGX-113-1602

- A pivotal Phase 3 study ARGX-113-1704

- An ongoing, open-label study ARGX-113-1705 (data cut-off date 01 February 2021).

Table 19 – Clinical studies with efgartigimod supporting the clinical efficacy of efgartigimod in generalized Myasthenia Gravis

Study Number/ Status	Primary Objective	IMP	Study Duration	Patients Analyzed
ARGX-113-1704/ Completed (Last patient completed: 06 April 2020)	To evaluate the efficacy of efgartigimod in the AChR-Ab seropositive population as assessed by the percentage of MG-ADL responders during C1	efgartigimod IV 10 mg/kg or matched placebo	Up to 28 weeks including a 2-week screening period	efgartigimod: N=84 placebo: N=83
ARGX-113-1705/ Ongoing (Data cutoff: 01 February 2021; Interim analysis 3)	To evaluate the long-term safety and tolerability of efgartigimod in AChR-Ab seropositive patients	efgartigimod IV 10 mg/kg	Part A: 1 year Part B: 2 years	efgartigimod-efgartigimod[a]: N=73 placebo-efgartigimod[b]: N=66 total efgartigimod[c]: N=139
ARGX-113-1602/ Completed (Last patient completed: 20 October 2017)	To evaluate the safety and tolerability of efgartigimod	efgartigimod IV 10 mg/kg or matched placebo	11 weeks	efgartigimod: N=12 placebo: N=12

AChR-Ab=anti-acetylcholine receptor antibody; C1=cycle 1; IMP=investigational medicinal product; IV=intravenous; MG-ADL=Myasthenia Gravis Activities of Daily Living; N=number of patients

[a] Efgartigimod-efgartigimod cohort: In study ARGX-113-1705, the efgartigimod-efgartigimod cohort refers to patients who received efgartigimod in antecedent study ARGX-113-1704 and efgartigimod in extension study ARGX-113-1705.

[b] Placebo-efgartigimod cohort: In study ARGX-113-1705, the placebo-efgartigimod cohort refers to patients who received placebo in antecedent study ARGX-113-1704 and efgartigimod in extension study ARGX-113-1705.

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

2.6.5.1. Dose response studies

Results of the phase 1 studies in healthy subjects (ARGX-113-1501 and ARGX-113-1702), the clinical studies in patients with gMG (ARGX-113-1602, ARGX-113-1704 and ARGX-113-1705), as well as PK/PD modelling analysis, indicate that a dose of efgartigimod 10 mg/kg, administered after 4 once weekly IV infusions achieved close to maximal IgG reduction.

Following a single infusion, up to a dose of 10 mg/kg a dose-dependent decrease of IgG levels was observed, while higher doses (i.e. 25 or 50 mg/kg) did not result in statistically significantly different IgG reductions. Similarly, following 4 once weekly infusions of 10 mg/kg or 25 mg/kg, no significant differences in the total IgG reductions were observed. In addition, similar effects on total IgG reduction were observed after a q4d or q7d dosing regimen of 10 mg/kg. Thus, dosing higher or more frequently than 4 weekly doses of efgartigimod IV 10 mg/kg is not expected to result in an improved PD effect (i.e. further decreases in autoantibody levels) and/or clinical effect and may be associated with a less optimal risk/benefit ratio. Lower dosing is expected to result in a lower PD effect and, thus, is likely to result in a less consistent and/or incomplete clinical response.

MG-ADL total score improvements followed a similar time course as total IgG and AChR-Ab reduction. In a proportion of patients, the duration of the clinical effect extended beyond the reduction of the PD markers (duration of response ≥12 weeks in 34% of AChR-Ab seropositive MG-ADL responders, which extended the time until a next cycle was initiated. In subsequent cycles, the time course and magnitude in total IgG and AChR-Ab reduction were consistently repeated.

In study ARGX-113-1704 for AChR-Ab seropositive patients, there were mean maximum reductions of 61,3% (SD 0.9) in IgG and 57,6% (1.3) in acetylcholine receptor antibodies, 1 week after the fourth infusion in cycle 1. Levels returned to baseline by week 12 (9 weeks after the last infusion of cycle 1). Reductions were similar across subtypes, with mean maximum reductions of 68% (1.0) for IgG1, 60% (1.7) for IgG2, 63% (1.2) for IgG3, and 52% (1·7) for IgG4. Similar reductions in IgG and acetylcholine receptor antibodies were seen with each treatment cycle. However, no reductions in albumin levels were observed.

Re-treatment with subsequent cycles of weekly infusions of efgartigimod IV 10 mg/kg for 4 weeks based on clinical evaluation is considered the most appropriate dose regimen for patients with gMG.

2.6.5.2. Main study

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness

Methods

The completed pivotal study ARGX-113-1704 is a phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicenter study conducted to evaluate the efficacy, safety, tolerability, quality of life, and impact on normal daily activities in patients with gMG who were treated with efgartigimod.

Approximately 150 patients were planned to be randomised in a 1:1 ratio to receive treatment cycles (TCs) of either efgartigimod IV 10 mg/kg or matched placebo infusions concomitantly with their existing gMG therapies; subsequent TCs were administered according to clinical response based on MG-ADL assessment. Patients were stratified according to 3 factors:

• AChR-Ab status (seropositive or seronegative; 20% of AChR-Ab seronegative patients' maximum)

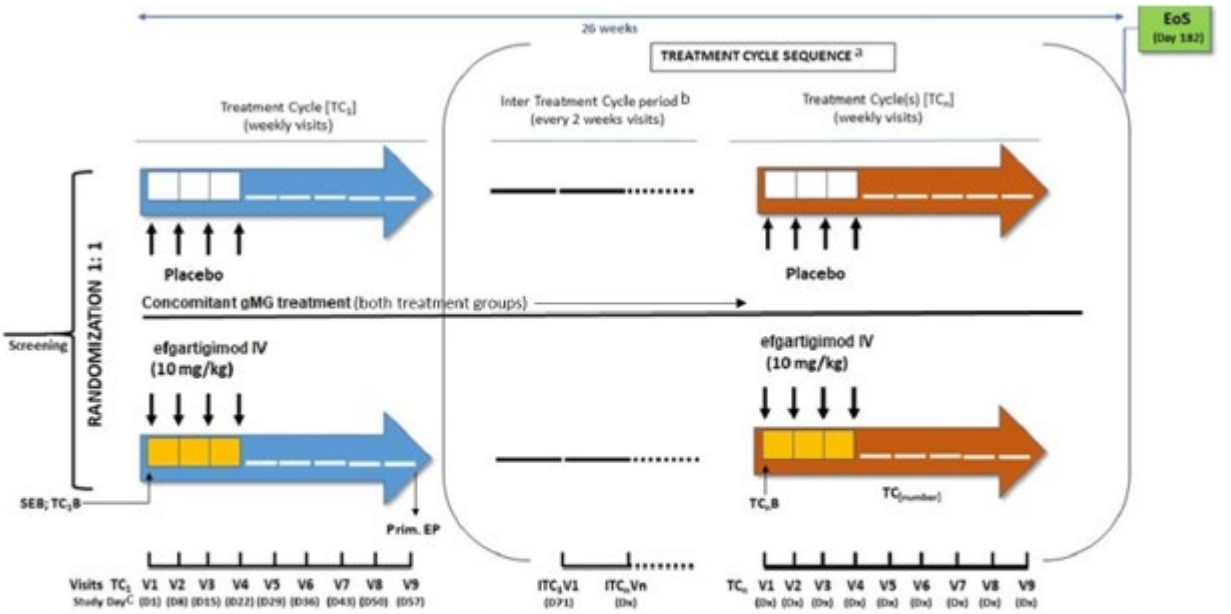
• Individual's concomitant treatment for gMG (nonsteroidal immunosuppressive drugs/NSIDs or not NSIDs)

• Japanese or non-Japanese

The total study duration was up to 26 weeks with an additional 2-week screening period. It included an initial 8-week TC (a 3-week treatment period and a 5-week follow-up period) when all randomised patients were treated with IMP/Placebo, which was followed by an inter-TC period of variable length depending on the patient's clinical response to efgartigimod (as measured by a total MG-ADL score of ≥5 points with more than 50% of the total score due to non-ocular symptoms) (Figure 16). At the end of each TC, patients received only concomitant gMG treatment, and the frequency of visits to the clinic was reduced from weekly to every 2 weeks.

Patients continued to receive concomitant gMG therapies (e.g. NSIDs, steroids, and AChE inhibitors); changes were not permitted to type or dosage, even if used for indications other than gMG. Rescue therapy was permitted if the patient deteriorated based on the Investigator's overall clinical assessment. Patients who required rescue therapy were discontinued from the study.

Patients who completed the study were eligible to enter the extension study ARGX-113-1705 and receive open-label efgartigimod IV 10 mg/kg.



D=day; EoS=end of study; gMG=generalized myasthenia gravis; ITC=intertreatment cycle; IV=intravenous; Prim. EP=primary endpoint; SEB=study entry baseline; TC=treatment cycle; TCB=treatment cycle baseline; V=visit

[a] The cycle sequence could have been repeated as many times as necessary as long as the last TC did not begin after day 127.

[b] The ITC period varied from patient to patient

[c] Time windows for clinic visits were ±1 day for TC visits and ±2 days for ITC visits.

Note: Cycle = TC + ITC

Figure 16 – Study schematic

- **Study Participants**

This study was conducted at 56 sites in 15 countries worldwide. Approximately 150 patients (maximum of 20% AChR-Ab seronegative patients) were planned to be enrolled. MG is considered an IgG autoantibody-driven disease even in patients for whom the antibody cannot be detected. Therefore, both AChR-Ab seropositive and seronegative patients were enrolled in study ARGX-113-1704.

Diagnosis and main criteria for inclusion

- Male or female patients aged ≥18 years
- Diagnosis of MG with generalized muscle weakness; Myasthenia Gravis Foundation of America (MGFA) class II, III, IVa, and IVb.

  The confirmation of the diagnosis was documented and supported by at least 1 of the following 3 tests:

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

  - history of positive edrophonium chloride test

  - patient has demonstrated improvement in MG signs on oral AChE inhibitors as assessed by the treating physician

- A MG-ADL total score of ≥5 points at screening and baseline with >50% of the total score attributed to non-ocular symptoms
- Patients were required to be on a stable dose of standard of care (concomitant gMG treatment) prior to screening. Concomitant gMG treatment was limited to acetylcholinesterase (AChE) inhibitors, steroids, and NSIDs with the following stability dose conditions:

  - NSIDs (e.g. azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment was to have started at least 6 months prior to screening and with no changes in dose in the 3 months before screening

  - steroids: treatment was to have started at least 3 months before screening and no changes in dose 1 month before screening

  - AChE inhibitors: stable dose with no dose escalation in the past 2 weeks before screening

The patient was to stop administration of an AChE inhibitors for at least 12 hours before the QMG assessment, as consistent with the revised manual for the QMG test recommended by the MGFA.

Main Exclusion Criteria

-Related to MG:

- MGFA Class I and V patients
- Patients with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, fluoroquinolones, beta-blockers, etc.)
- Patients with documentation of a lack of clinical response to PLEX

- Related to Previous or Concomitant Treatments:

- IGs given by IV (IVIg), subcutaneous, or intramuscular route; or PLEX each within 1 month prior to screening.
- Use of any monoclonal antibody, such as rituximab and eculizumab, within 6 months prior to first dose
- Thymectomy when performed <3 months prior to screening or planned to be performed during the study period
- Use of investigational drug within 3 months or 5 half-lives of the drug (whichever was longer) prior to screening
- Patients who previously participated in a clinical study with efgartigimod

- Related to Infection and Malignancy Risk Factors:

- Patients with known seropositivity or who tested positive for an active viral infection at screening with hepatitis B virus, hepatitis C virus, HIV
- Patients with any known severe bacterial, viral, or fungal infection or any major episode of infection that required hospitalisation or injectable antimicrobial therapy in the last 8 weeks prior to screening
- Patients with total IgG level <6 g/L at screening
- Patients who received a vaccination (e.g. influenza vaccine) within the last 4 weeks prior to screening
- Patients who had a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders, unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before screening

- Other:

- Patients with a known autoimmune disease other than MG (for example, autoimmune thyroiditis, rheumatoid arthritis) that would interfere with an accurate assessment of clinical symptoms.
- Patients with clinical evidence of other significant serious disease or patients who underwent a recent major surgery, which could confound the results of the study or put the patient at undue risk. Patients with renal/hepatic function impairment were included.
- Pregnant and lactating women, and those intending to become pregnant during the study or within 90 days after the last dosing. Women of childbearing potential and male patients were to use a highly effective method of contraception (ie, pregnancy rate of less than 1% per year).

The following medications and treatments were not permitted during the study and were to result in study discontinuation if they had been received:

- any other IgG therapy
- change in the type or dose/regimen of concomitant treatment (replacing, adding, or removing treatment, or adjusting dose and/or frequency of established treatment), even if used for indications other than gMG
- any monoclonal antibody for immunomodulation
- vaccines
- rescue therapy.

In addition, IMP was discontinued if any of the following occurred:

- Randomisation code was broken prematurely (resulted in study discontinuation)
- Patient became pregnant
- Patient developed a serious adverse event (SAE) that could jeopardize the safety of the patient
- Patients with clinical evidence of bacterial, viral, or fungal disease or any other significant disease that could confound the results of the study or put the patient at undue risk. In these patients, the decision to temporarily interrupt or discontinue treatment was made on a case by case basis

Patients who withdrew or were withdrawn from the study were not replaced. Patients who discontinue from randomised treatment and who do not withdraw consent were followed for safety and disease severity assessments.

- **Treatments**

Efgartigimod IV 10 mg/kg or matching placebo was intravenously administered as a 1-hour infusion every 7 days (q7d) for 4 infusions. The total dose per IMP infusion is capped at 1200 mg for patients with body weight ≥120 kg.

Duration of treatment was up to 26 weeks, an initial 8-week TC, and ITCs of variable length depending on the patient's clinical response to efgartigimod.

To be retreated, a patient must have met all of the following retreatment criteria:

- completed the prior TC (ie, the 3-week treatment period and the 5-week follow-up period)

- the MG-ADL total score ≥5 points with >50% of the total score attributed to non-ocular symptoms

  OR if the patient was an MG-ADL responder in a previous cycle and lost the response (defined as a <2-point reduction in the MG-ADL total score in Cn compared to baseline)

- the subsequent cycle must have started no later than day 127 and have been completed within the 26-week study duration

Rescue therapy was permitted for patients with protocol-defined MG clinical deterioration (new or worsening of respiratory/bulbar symptoms or a ≥2-point increase in individual non-ocular items on the MG-ADL scale) and for whom the Investigator considered the patient's health to be in jeopardy if rescue therapy was not provided. The following treatments were considered rescue therapy: PLEX, IVIg, immunoadsorption, any new type of corticosteroid, an increased dose of current corticosteroid uses as stand-alone therapy or in combination with another treatment. In situations where rescue therapy is given, patients were discontinued early from randomized treatment.

The patient was to receive 4 IMP infusions in each cycle. If a dose was delayed for more than 3 days, then that dose was not administered to ensure that 2 consecutive doses were administered with an interval of at least 3 days apart. Patients who missed doses remained in the study.

- **Objectives**

Primary

- To evaluate the efficacy of efgartigimod as assessed by the percentage of Myasthenia Gravis – Activities of Daily Living (MG-ADL) responders after the first treatment cycle (TC) in the acetylcholine receptor-antibody (AChR-Ab) seropositive population

Secondary

- To evaluate the efficacy of efgartigimod as assessed by the percentage of Quantitative Myasthenia Gravis (QMG) responders after the first TC in the AChR-Ab seropositive population
- To evaluate the efficacy of efgartigimod as assessed by the percentage of MG-ADL responders after the first TC in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients)
- To evaluate the efficacy of efgartigimod as assessed by the percentage of time that patients show a clinically meaningful improvement (CMI) in the MG-ADL total score during the study (up to and including day 126) in the AChR-Ab seropositive population
- To evaluate the efficacy of efgartigimod as assessed by the time to qualification for first retreatment in the AChR-Ab seropositive population
- To evaluate the onset of efficacy of efgartigimod as assessed by the percentage of early MG-ADL responders after the first TC in the AChR-Ab seropositive population
- To evaluate the safety and tolerability of efgartigimod in the overall population and in Subgroups

Tertiary Objective

- To assess additional efficacy and safety parameters, pharmacodynamics (PD), and immunogenicity

- **Outcomes/endpoints**

The primary endpoint was the percentage of patients who, after the first treatment cycle (TC1), had a reduction of at least 2 points on the MG-ADL total score (compared to baseline of the first cycle [TC1B]) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the investigational medicinal product (IMP) in the active versus placebo group in AChR-Ab seropositive population.

The proportion of MG-ADL responders in the placebo group was hypothesised to be 30%. The treatment difference was assumed to be 35% for acetylcholine receptor antibody-positive patients and 5% for acetylcholine receptor antibody-negative patients. A difference of total MG-ADL responder rate of 35% between the placebo and efgartigimod primary acetylcholine receptor antibody-positive population is considered clinically relevant. In the phase 2 ARGX-113-1602 study, the total MG-ADL responder rate was 33% for placebo (three of 12) and 75% (nine of 12) for efgartigimod. Sample size was based on allowing enrolment of up to 20% acetylcholine receptor antibody-negative patients. Based on this quota, a sample size of 150 provided power of 96% in the primary population of acetylcholine receptor antibody-positive patients to detect a difference of 35% in the proportion of responders with 120 patients. The sample size also provided a power of 90% to detect a 29% difference in the proportion of responders in the overall population with a two-sided α level of 5%, allowing for a 10% dropout rate.

The secondary endpoints were:

1. Percentage of patients who, after the first treatment cycle, have a decrease of at least 3 points on the total QMG score (compared to TC1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion in the active versus placebo group in AChR-Ab seropositive patients.
2. Percentage of patients who, after the first treatment cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP group in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients)
3. Percentage of time that patients have a clinically meaningful improvement in MG-ADL total score compared to study entry baseline (SEB) during the study (up to and including day 126) in the active versus placebo group in AChR-Ab seropositive patients
4. Time from week 4 to qualify for retreatment, as assessed by monitoring the total MG-ADL score compared to TC1B (ie, the patient has <2-point reduction in the MG-ADL total score and MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms), in the active versus placebo group in the AChR Ab seropositive population
5. Percentage of patients who, after the first treatment cycle, have a decrease of at least 2 points on the MG-ADL total score (compared to TC1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest after 1 or maximum 2 infusions of IMP (early MG-ADL responders) in the active versus placebo group in the AChR-Ab seropositive patients. In practice, visit week 2 is the last visit the onset of response can start to be considered an early responder, even in case of a missed infusion.

The MG-QoL15r and MGC were used as tertiary or exploratory endpoints.

- **Sample size**

Approximately 150 patients and a maximum of 20% AChR-Ab seronegative patients were planned, considering a 10% attrition rate. The study was powered at 90% using a significance level of 5% 2-sided to test the alternative hypothesis of the difference in the percentage of responders would be 29% in favor of efgartigimod patients. The 29% is a weighted average of 80% AChR-Ab seropositive patients with a treatment difference of 35% and 20% AChR-Ab seronegative patients with a treatment difference

of 5%. The percentage MG-ADL responders in patients in the placebo group has been hypothesized as 30%.

No interim analysis was performed for this study,

- **Randomisation and Blinding (masking)**

Patients were randomised in a 1:1 ratio and were stratified according to 3 factors: AChR-Ab status (seropositive or seronegative; 20% of AChR-Ab seronegative patients' maximum), individual's concomitant treatment for gMG (nonsteroidal immunosuppressive drugs/NSIDs or not NSIDs), Japanese or non-Japanese.

The investigator and staff at clinical sites as well as the sponsor were blinded to patient treatment assignment and PK, PD, and anti-drug antibody (ADA) data.

- **Statistical methods**

The efficacy endpoints were tested in the modified Intention-To-Treat (mITT) and the Per Protocol (PP) populations.

- Modified intention-to-treat (mITT): all randomized patients with a value for the MG-ADL total score at baseline and at least 1 postbaseline timepoint. Efficacy and PD analyses were based on the mITT analysis set.
- Per protocol (PP): a subset of the mITT set of patients with ≥3 out of 4 infusions (in any order) without a major protocol deviation reported. The PP analysis set was used for sensitivity analyses of primary and secondary endpoints.

The primary endpoint is tested by means of a 2-sided test (using exact logistic regression) stratified for the stratification factors Japanese/non-Japanese patient, AChR-Ab serotype and SoC (NSID versus no NSID as concomitant gMG treatment) at the 2-sided 5% significance level, in the AChR-Ab seropositive patients. Percentage responders will be compared between ARGX-113 and placebo using logistic regression model with Baseline MG-ADL total score as covariate and Japanese/non-Japanese patient, AChR-Ab serotype (where applicable) and SoC as stratification variables. The treatment effect has been presented as the odds ratio (OR) and the approximate 95% confidence interval (CI) limits was based on maximum likelihood estimates of logistic parameters.

To control the type I error, the primary efficacy endpoint was the gatekeeper for the testing of secondary endpoints. The primary endpoint and secondary endpoints were tested in strict hierarchical order to control the type I error. A statistically significant difference (two-sided, 5% alpha) between efgartigimod and placebo had to be found in the endpoint result before the next endpoint to be tested.

Sensitivity analyses of primary endpoint included: Per protocol set, patients with or without thymectomy, missing-is-failure imputation.

Subgroup analyses were run on the primary outcome for demographic characteristics: age, gender, region, antibody status etc. The analysis for antibody status is also run without the interaction term on the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

Results

- **Participant flow**

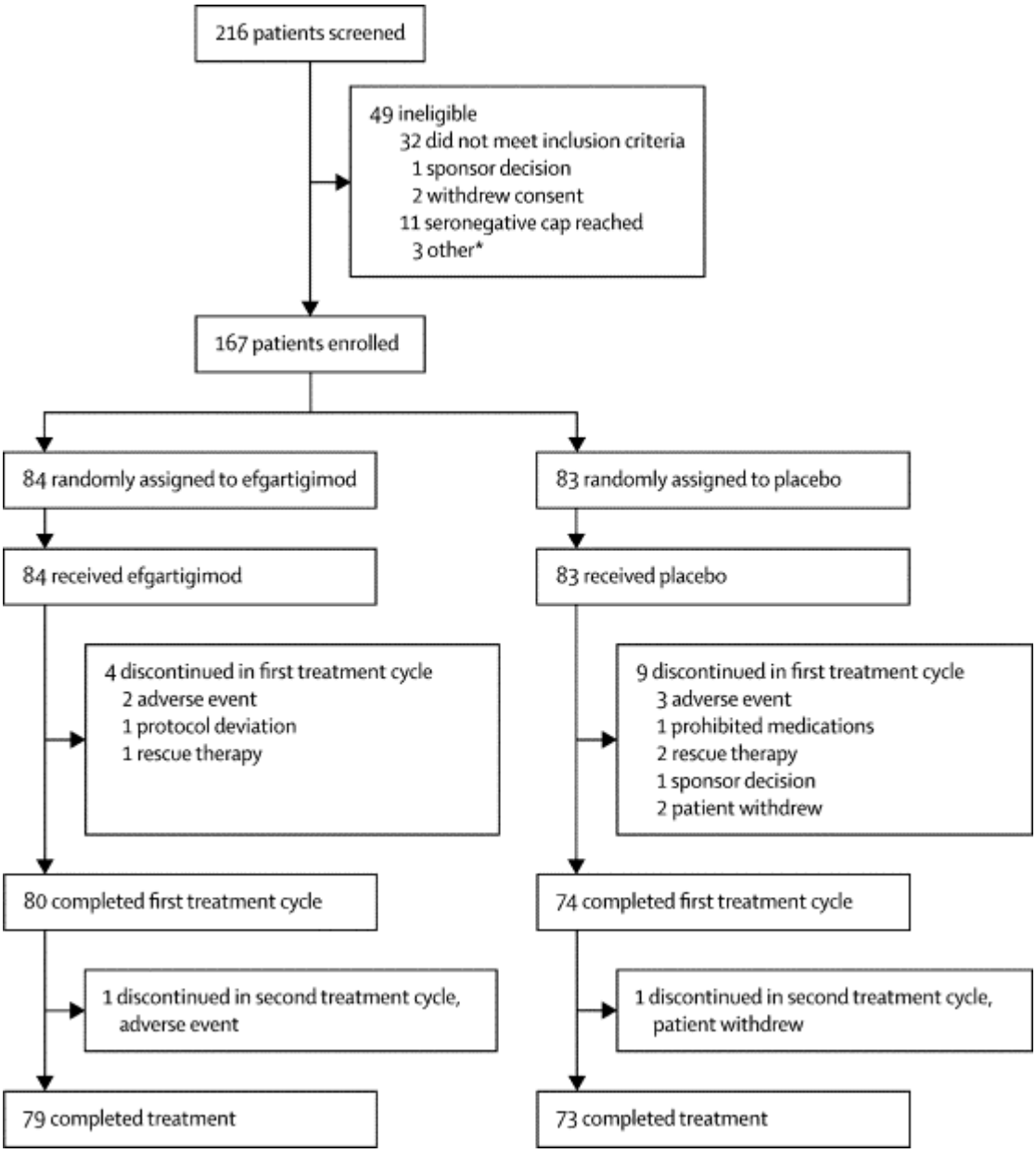
Of the 216 patients screened for inclusion, 167 patients were enrolled and randomised to receive IMP. There were 129 (77.2%) AChR-Ab seropositive patients (in both the modified intent-to-treat and safety analyses sets), and 38 (22.8%) AChR-Ab seronegative patients.

Patient disposition is summarised in Figure below. Overall, 152 (91.0%) patients completed treatment and 156 (93.4%) patients completed the study.

The mean (SD) duration in the study (ie, period starting from the first dose until the end of study) was comparable between the treatment groups; 151.5 (22.4) days in the efgartigimod group and 151.7 (29.6) days in the placebo group.

Patients in either group received a maximum of 3 treatment cycles. The number of patients/treatment cycles was balanced between the efgartigimod group. The duration of each cycle was similar between efgartigimod and placebo; the median (min, max) duration was 72.0 (16, 190) days for C1, 71.0 (56, 127) days for C2, and 58 (15, 67) days for C3. For most AChR-Ab seropositive patients, cycles 1 and 2 lasted 10 weeks (45.0% and 61.7% patients, respectively) and C3 lasted 8 weeks (62.5%).

The cumulative duration of treatment exposure was 34.86 patient-years for the efgartigimod group and 34.51 patient-years for the placebo group in study ARGX-113-1704.



- **Recruitment**

Date first patient enrolled: 22 Aug 2018. Date last patient completed: 06 Apr 2020. Database lock eCRF data: 13 May 2020.

- **Conduct of the study**

The original protocol was dated 16 June 2018. There have been 2 substantial amendments to the original master protocol (version 2.0 on 28 Nov 2018, version 3.0 on 11 July 2019). The statistical analysis plan had 2 versions and version 2 was finalised on 8 May 2020 before the database lock.

During the conduct of the study discrepancies were identified in a number of the enrolled patients between the sites reporting of historical AChR antibody status and the results from the central laboratory test. Specifically, some patients were reported as having a previous test identifying them as AChR-Ab seropositive whereas the central laboratory test identified them as being AChR-Ab seronegative. As defined in the protocol, the central laboratory result was used for patient stratification.

- **Baseline data**

Patient demographics of the study population are summarised in Table 20.

Table 20 – Patient demographics (safety analysis set)

	All Patients		AChR-Ab Seropositive		AChR-Ab Seronegative	
	Efgartigimod (N=84)	Placebo (N=83)	Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod (N=19)	Placebo (N=19)
Age (years)						
n	84	83	65	64	19	19
Mean (SD)	45.9 (14.41)	48.2 (14.97)	44.7 (14.97)	49.2 (15.54)	50.2 (11.61)	44.8 (12.63)
Median (min, max)	45.0 (19, 78)	46.0 (19, 81)	43.0 (19, 78)	46.5 (19, 81)	49.0 (28, 75)	43.0 (19, 76)
Age category, n (%)						
18 – <65 years	73 (86.9)	69 (83.1)	57 (87.7)	51 (79.7)	16 (84.2)	18 (94.7)
≥ 65 years	11 (13.1)	14 (16.9)	8 (12.3)	13 (20.3)	3 (15.8)	1 (5.3)
Sex at birth, n (%)						
Female	63 (75.0)	55 (66.3)	46 (70.8)	40 (62.5)	17 (89.5)	15 (78.9)
Male	21 (25.0)	28 (33.7)	19 (29.2)	24 (37.5)	2 (10.5)	4 (21.1)
Race, n (%)						
American Indian or Alaska native	2 (2.4)	0	2 (3.1)	0	0	0
Asian	9 (10.7)	7 (8.4)	7 (10.8)	4 (6.3)	2 (10.5)	3 (15.8)
Black or African American	3 (3.6)	3 (3.6)	1 (1.5)	3 (4.7)	2 (10.5)	0
White	69 (82.1)	72 (86.7)	54 (83.1)	56 (87.5)	15 (78.9)	16 (84.2)
Multiple	1 (1.2)	0	1 (1.5)	0	0	0
Not reported	0	1 (1.2)	0	1 (1.6)	0	0
Ethnicity, n (%)						
Japanese	8 (9.5)	7 (8.4)	6 (9.2)	4 (6.3)	2 (10.5)	3 (15.8)
Hispanic or Latino	7 (8.3)	2 (2.4)	5 (7.7)	2 (3.1)	2 (10.5)	0
Not Hispanic or Latino	69 (82.1)	73 (88.0)	54 (83.1)	57 (89.1)	15 (78.9)	16 (84.2)
Not reported	0	1 (1.2)	0	1 (1.6)	0	0
Weight (kg)						
n	84	83	65	64	19	19
Mean (SD)	81.80 (27.660)	78.39 (19.176)	81.61 (29.823)	79.51 (19.521)	82.43 (19.101)	74.59 (17.931)
Median (min, max)	76.05 (49.0, 228.7)	74.00 (41.2, 118.1)	74.00 (49.0, 228.7)	74.20 (41.2, 118.1)	80.20 (55.4, 132.0)	72.60 (46.0, 115.0)

Source: Section 14, Tables 14.1.2.1.1, 14.1.2.1.2, 14.1.2.1.3
AChR-Ab=acetylcholine receptor antibody; max=maximum; min=minimum; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; SD=standard deviation

Ethnicity, n (%)						
Japanese	8 (9.5)	7 (8.4)	6 (9.2)	4 (6.3)	2 (10.5)	3 (15.8)
Hispanic or Latino	7 (8.3)	2 (2.4)	5 (7.7)	2 (3.1)	2 (10.5)	0
Not Hispanic or Latino	69 (82.1)	73 (88.0)	54 (83.1)	57 (89.1)	15 (78.9)	16 (84.2)
Not reported	0	1 (1.2)	0	1 (1.6)	0	0
Weight (kg)						
n	84	83	65	64	19	19
Mean (SD)	81.80 (27.660)	78.39 (19.176)	81.61 (29.823)	79.51 (19.521)	82.43 (19.101)	74.59 (17.931)
Median (min, max)	76.05 (49.0, 228.7)	74.00 (41.2, 118.1)	74.00 (49.0, 228.7)	74.20 (41.2, 118.1)	80.20 (55.4, 132.0)	72.60 (46.0, 115.0)

Source: Section 14, Tables 14.1.2.1.1, 14.1.2.1.2, 14.1.2.1.3
AChR-Ab=acetylcholine receptor antibody; max=maximum; min=minimum; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; SD=standard deviation

Disease characteristics at baseline are summarised in Table 21 for the AChR-Ab seropositive, AChR-Ab seronegative, and overall populations.

Table 21 – Baseline disease characteristics (safety analysis set)

	AChR-Ab Seropositive		AChR-Ab Seronegative		Overall		
	Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod (N=19)	Placebo (N=19)	Efgartigimod (N=84)	Placebo (N=83)	Total N=167
Time since diagnosis (years)							
n	65	64	19	19	84	83	167
Mean (SD)	9.68 (8.251)	8.93 (8.214)	11.68 (11.461)	8.50 (5.225)	10.13 (9.038)	8.83 (7.606)	9.48 (8.358)
Median (min, max)	7.36 (1.0, 45.3)	6.15 (0.2, 36.1)	8.81 (0.9, 51.8)	8.26 (1.4, 17.5)	8.17 (0.9, 51.8)	6.86 (0.2, 36.1)	7.36 (0.2, 51.8)
Thymectomy for MG, n (%)							
n (%)	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167
No	20 (30.8)	34 (53.1)	5 (26.3)	13 (68.4)	25 (29.8)	47 (56.6)	72 (43.1)
Yes	45 (69.2)	30 (46.9)	14 (73.7)	6 (31.6)	59 (70.2)	36 (43.4)	95 (56.9)
mean (SD) time (years) since thymectomy	10.31 (8.270)	11.56 (8.822)	12.88 (12.584)	6.43 (3.581)	10.92 (9.412)	10.71 (8.372)	10.84 (8.987)
MGFA class at screening, n (%)							
n (%)	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167 (100)
Class II – IIa	14 (21.5)	14 (21.9)	2 (10.5)	3 (15.8)	16 (19.0)	17 (20.5)	33 (19.8)
Class II – IIb	14 (21.5)	11 (17.2)	4 (21.1)	3 (15.8)	18 (21.4)	14 (16.9)	32 (19.2)
Class III – IIIa	15 (23.1)	19 (29.7)	5 (26.3)	6 (31.6)	20 (23.8)	25 (30.1)	45 (26.9)
Class III – IIIb	20 (30.8)	17 (26.6)	7 (36.8)	7 (36.8)	27 (32.1)	24 (28.9)	51 (30.5)
Class IV – IVa	1 (1.5)	3 (4.7)	0	0	1 (1.2)	3 (3.6)	4 (2.4)
Class IV – IVb	1 (1.5)	0	1 (5.3)	0	2 (2.4)	0	2 (1.2)
MG-ADL total score							
n	65	64	19	19	84	83	167
Mean (SD)	9.0 (2.48)	8.6 (2.14)	9.7 (3.12)	9.8 (2.51)	9.2 (2.64)	8.8 (2.28)	9.0 (2.46)
Median (min, max)	9.0 (5, 15)	8.0 (5, 16)	8.0 (6, 17)	10.0 (6, 14)	9.0 (5, 17)	9.0 (5, 16)	9.0 (5, 17)
MG-ADL total score category, n (%)							
n (%)	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167 (100)
5-7	16 (24.6)	18 (28.1)	4 (21.1)	4 (21.1)	20 (23.8)	22 (26.5)	42 (25.1)
8-9	25 (38.5)	29 (45.3)	6 (31.6)	5 (26.3)	31 (36.9)	34 (41.0)	65 (38.9)
≥10	24 (36.9)	17 (26.6)	9 (47.4)	10 (52.6)	33 (39.3)	27 (32.5)	60 (35.9)
Total QMG score							
n	65	62	19	19	84	81	165
Mean (SD)	16.0 (5.14)	15.2 (4.39)	16.6 (4.62)	16.5 (5.20)	16.2 (5.01)	15.5 (4.59)	15.9 (4.80)
Median (min, max)	16.0 (4, 28)	15.5 (6, 24)	17.0 (8, 25)	16.0 (8, 27)	17.0 (4, 28)	16.0 (6, 27)	16.0 (4, 28)
Total MGC							
n	65	64	19	19	84	83	167
Mean (SD)	18.6 (6.08)	18.1 (5.18)	19.3 (6.18)	19.1 (6.41)	18.8 (6.07)	18.3 (5.46)	18.5 (5.76)
Median (min, max)	19.0 (3, 33)	18.0 (8, 29)	20.0 (10, 32)	20.0 (4, 29)	19.0 (3, 33)	18.0 (4, 29)	19.0 (15.0, 23.0)
Concomitant gMG treatment (actual), n (%)							
n (%)	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167 (100)
NSIDs	40 (61.5)	37 (57.8)	11 (57.9)	14 (73.7)	51 (60.7)	51 (61.4)	102 (61.1)
No NSIDs	25 (38.5)	27 (42.2)	8 (42.1)	5 (26.3)	33 (39.3)	32 (38.6)	65 (38.9)
AChR-Ab status (actual), n (%)							
n	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167 (100)
Positive	65 (100)	64 (100)	0	0	65 (77.4)	64 (77.1)	129 (77.2)
Negative	0	0	19 (100)	19 (100)	19 (22.6)	19 (22.9)	38 (22.8)
MuSK-Ab status, n (%)							
n	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)	167 (100)
Positive	0	0	3 (15.8)	3 (15.8)	3 (3.6)	3 (3.6)	6 (3.6)
Negative	65 (100)	64 (100)	16 (84.2)	16 (84.2)	81 (96.4)	80 (96.4)	161 (96.4)

Source: Section 14, Tables 14.1.2.2.1, 14.1.2.2.2, 14.1.2.2.3

AChR-Ab=acetylcholine receptor - antibody; max=maximum; MG=myasthenia gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; MGFA=Myasthenia Gravis Foundation of America; min=minimum; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; NSID=nonsteroidal immunosuppressive drug; QMG=Quantitative Myasthenia Gravis; MuSK-Ab=muscle specific tyrosine kinase antibody

Note: Ranges of the clinical outcome assessments are as follows: MG-ADL total score 0-24, QMG score 0-39, MGC 0-50, and MG-QoL15r 0-30; for each instrument, higher scores are indicative of more severe disease.

Treatments and Medications:

Table 22 – Prior therapy for generalized Myasthenia Gravis (safety analysis set)

	AChR-Ab Seropositive		AChR-Ab Seronegative		Overall	
	Efgartigimod (N=65) n (%)	Placebo (N=64) n (%)	Efgartigimod (N=19) n (%)	Placebo (N=19) n (%)	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
≥1 prior gMG therapy	65 (100)	64 (100)	19 (100)	19 (100)	84 (100)	83 (100)
≥2 prior gMG therapy	61 (93.8)	63 (98.4)	15 (78.9)	17 (89.5)	76 (90.5)	80 (96.4)
≥3 prior gMG therapy	49 (75.4)	53 (82.8)	11 (57.9)	16 (84.2)	60 (71.4)	69 (83.1)
≥1 prior NSID therapy	47 (72.3)	43 (67.2)	15 (78.9)	14 (73.7)	62 (73.8)	57 (68.7)
≥2 prior NSID therapy	13 (20.0)	10 (15.6)	1 (5.3)	3 (15.8)	14 (16.7)	13 (15.7)
≥3 prior NSID therapy	2 (3.1)	4 (6.3)	1 (5.3)	1 (5.3)	3 (3.6)	5 (6.0)

Source: Section 14, Tables 14.1.2.8.1, 14.1.2.8.2, 14.1.2.8.3
AChR-Ab=acetylcholine receptor - antibody; gMG=generalized myasthenia gravis; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; NSID=nonsteroidal immunosuppressive drug

Table 23 – Concomitant therapy and treatment classes for gneralized Myasthenia Gravis (safety analysis set)

	AChR-Ab Seropositive		AChR-Ab Seronegative		Overall	
	Efgartigimod (N=65) n (%)	Placebo (N=64) n (%)	Efgartigimod (N=19) n (%)	Placebo (N=19) n (%)	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Any steroid	46 (70.8)	51 (79.7)	14 (73.7)	16 (84.2)	60 (71.4)	67 (80.7)
hydrocortisone	0	1 (1.6)	1 (5.3)	0	1 (1.2)	1 (1.2)
methylprednisolone	8 (12.3)	7 (10.9)	1 (5.3)	6 (31.6)	9 (10.7)	13 (15.7)
prednisolone	9 (13.8)	14 (21.9)	3 (15.8)	4 (21.1)	12 (14.3)	18 (21.7)
prednisone	29 (44.6)	30 (46.9)	10 (52.6)	6 (31.6)	39 (46.4)	36 (43.4)
Any NSID	40 (61.5)	37 (57.8)	11 (57.9)	14 (73.7)	51 (60.7)	51 (61.4)
azathioprine	20 (30.8)	21 (32.8)	4 (21.1)	5 (26.3)	24 (28.6)	26 (31.3)
ciclosporin	11 (16.9)	9 (14.1)	2 (10.5)	2 (10.5)	13 (15.5)	11 (13.3)
cyclophosphamide	2 (3.1)	2 (3.1)	0	0	2 (2.4)	2 (2.4)
methotrexate	0	2 (3.1)	0	0	0	2 (2.4)
mycophenolate mofetil/mycophenolate sodium	7 (10.8)	3 (4.7)	4 (21.1)	4 (21.1)	11 (13.1)	7 (8.4)
tacrolimus	1 (1.5)	0	1 (5.3)	3 (15.8)	2 (2.4)	3 (3.6)
Any AChE inhibitor	57 (87.7)	57 (89.1)	14 (73.7)	10 (52.6)	71 (84.5)	67 (80.7)
ambenonium chloride/ambenonium	10 (15.4)	4 (6.3)	0	1 (5.3)	9 (10.7)	5 (6.0)
distigmine bromide/distigmine	1 (1.5)	3 (4.7)	0	0	1 (1.2)	3 (3.6)
neostigmine bromide	0	0	1 (5.3)	0	1 (1.2)	0
pyridostigmine bromide/pyridostigmine	49 (75.4)	53 (82.8)	13 (68.4)	9 (47.4)	62 (73.8)	62 (74.7)
One class	19 (29.2)	11 (17.2)	5 (26.3)	4 (21.1)	24 (28.6)	15 (18.1)
steroid	4 (6.2)	4 (6.3)	2 (10.5)	2 (10.5)	6 (7.1)	6 (7.2)
NSID	2 (3.1)	1 (1.6)	0	1 (5.3)	2 (2.4)	2 (2.4)
AChE inhibitor	13 (20.0)	6 (9.4)	3 (15.8)	1 (5.3)	16 (19.0)	7 (8.4)
Two classes	14 (21.5)	22 (34.4)	8 (42.1)	6 (31.6)	22 (26.2)	28 (33.7)
steroid + NSID	2 (3.1)	1 (1.6)	3 (15.8)	5 (26.3)	5 (6.0)	6 (7.2)
steroid + AChE inhibitor	8 (12.3)	16 (25.0)	3 (15.8)	1 (5.3)	11 (13.1)	17 (20.5)
NSID + AChE inhibitor	4 (6.2)	5 (7.8)	2 (10.5)	0	6 (7.1)	5 (6.0)
Three classes	32 (49.2)	30 (46.9)	6 (31.6)	8 (42.1)	38 (45.2)	38 (45.8)

Source: Section 14, Tables 14.1.2.9.1, 14.1.2.9.2, 14.1.2.9.3

AChE=acetylcholinesterase; AChR-Ab=acetylcholine receptor antibody; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; NSID=nonsteroidal immunosuppressive drug

Measurements of treatment compliance:

Table 24 – Patient percentage treatment compliance by cycle (safety analysis set)

	Efgartigimod (N=84)	Placebo (N=83)	Overall (N=167)
Cycle 1			
n	84	83	167
Mean (SD)	99.1 (6.07)	97.6 (10.77)	98.4 (8.74)
Median (min, max)	100.0 (50, 100)	100.0 (25, 100)	100.0 (25, 100)
Cycle 2			
n	63	57	120
Mean (SD)	99.2 (4.42)	99.1 (6.62)	99.2 (5.55)
Median (min, max)	100.0 (75, 100)	100.0 (50, 100)	100.0 (50, 100)
Cycle 3			
n	7	3	10
Mean (SD)	82.1 (31.34)	100.0 (0.00)	87.5 (27.00)
Median (min, max)	100.0 (25, 100)	100.0 (100, 100)	100.0 (25, 100)

- **Numbers analysed**

Table 25 – Number of patients in each population or analysis set

	Efgartigimod n	Placebo n	Overall n
Screened			216
Randomized	84	83	167
Safety analysis set			
Overall	84	83	167
AChR-Ab seropositive	65	64	129
AChR-Ab seronegative	19	19	38
mITT analysis set			
Overall	84	83	167
AChR-Ab seropositive	65	64	129
AChR-Ab seronegative	19	19	38
Per protocol analysis set			
Overall	69	71	140
AChR-Ab seropositive	55	53	108
AChR-Ab seronegative	14	18	32

Source: Section 14, Table 14.1.1.1
AChR-Ab=acetylcholine receptor antibody; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported
Note: The actual treatment was used for the safety analysis set. The randomized treatment was used for the other analysis sets. The AChR-Ab seropositive and seronegative subpopulations were defined based on the stratification factor as randomized.
Note: The PK analysis set is defined in Section 11.4.4.1.1.

- **Outcomes and estimation**

The efficacy of efgartigimod was analysed using endpoints based on the following clinical outcome measures:

- MG-ADL (primary, secondary, tertiary, and exploratory endpoints)
- QMG (secondary, tertiary, and exploratory endpoints)
- MGC (exploratory endpoints)
- MG-QoL15r (tertiary and exploratory endpoints)

Primary and Secondary Efficacy Endpoints:

	Efgartigimod group	Placebo group	OR (95% CI)	p value
MG-ADL responder in cycle 1 (primary endpoint)	44/65 (68%)	19/64 (30%)	4·95 (2·21–11·53)	<0·0001
Quantitative Myasthenia Gravis responder in cycle 1	41/65 (63%)	9/64 (14%)	10·84 (4·18–31·20)	<0·0001
MG-ADL responder in cycle 1 (all patients)	57/84 (68%)	31/83 (37%)	3·70 (1·85–7·58)	<0·0001
Percentage of time with ≥2-point improvement in MG-ADL up to day 126	48·7%	26·6%	--	0·0001
Median time from day 28 until no clinically meaningful improvement, days	35 (18–71)	8 (1–57)	--	0·26
Early MG-ADL responder (cycle 1)	37/65 (57%)	16/64 (25%)	--	Not assessed*

Data are n/N (%), or median (IQR), unless stated otherwise. Analyses were done in acetylcholine receptor antibody-positive patients unless otherwise stated. MG-ADL=Myasthenia Gravis Activities of Daily Living. *Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not assessed because the fourth secondary endpoint was not significant.

Table 2: **Summary of primary and secondary endpoints**

Sensitivity Analysis MG-ADL Responders in the AChR-Ab Seropositive Population During Cycle 1

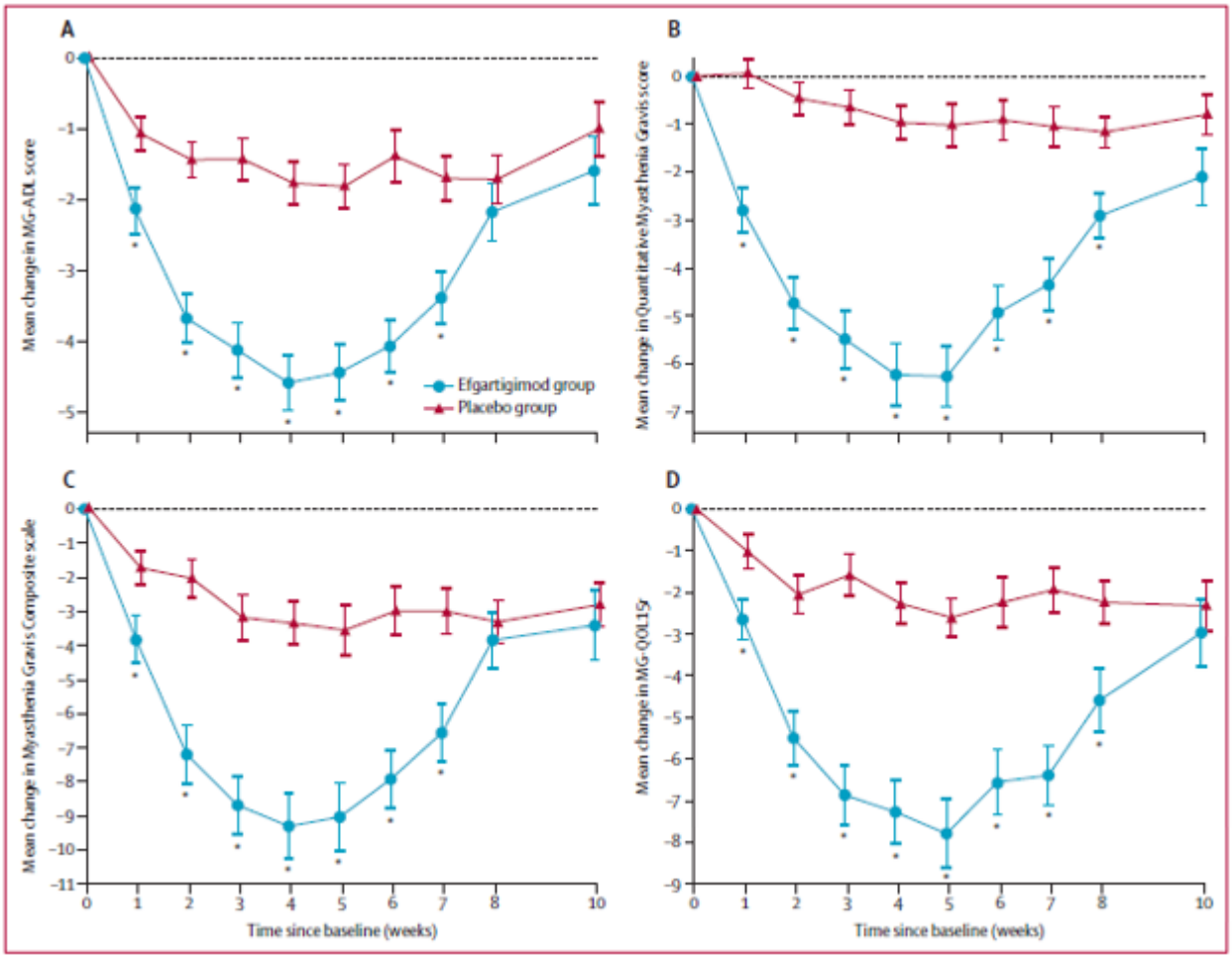
The primary endpoint was analysed using data from the PP population in a sensitivity analysis. In the AChR-Ab seropositive population, the MG-ADL responder criterion was met in 36 (65.5%) patients in the efgartigimod group compared to 18 (34.0%) patients in the placebo group during C1: OR (95% CI) =3.75 (1.585; 9.25) (p=0.0016; logistic regression testing).

The results of another sensitivity analysis to assess the imputation impact for missing values (using a missing-is-failure imputation) revealed 40 (61.5%) patients as MG-ADL responders in the efgartigimod group compared to 19 (29.7%) patients in the placebo group during C1: OR (95% CI) =3.75 (1.704; 8.524) (p=0.0006; logistic regression testing).

Exploratory Efficacy Endpoints:

The efficacy of efgartigimod was explored in other analyses of the MG-ADL and QMG outcome measures, and with the MGC and health-related quality of life questionnaires, the generic EQ-5D-5L, and the disease-specific MG-QoL15r.

In the AChR-Ab seropositive population, patients in the efgartigimod group had greater total mean score improvements in MG-ADL, QMG, MCG, and MG-QOL15r in cycle 1, with nominally significant differences from baseline observed from week 1 and sustained through week 7 (Figure 17). The maximum improvement in efgartigimod treated patients occurred at week 5 for MG-QOL15r and week 4 for other measures. The mean (95% CI) change from SEB 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.



Error bars show standard error. MG-ADL=Myasthenia Gravis Activities of Daily Living. MG-QOL15r=15-item revised version of the Myasthenia Gravis Quality of Life questionnaire. *p<0·05.

Figure 17 – Change in MG-ADL (A), Quantitative Myasthenia Gravis score (B), Myasthenia Gravis composite scale (C), and MG-QOL15r (D) during cycle 1, in acetylcholine receptor antibody-positive patients

Table 26 – Mean change from cycle baseline at week 4 in MG-ADL total score in study ARGX-113-1704 (mITT analysis set)

	AChR-Ab Seropositive				AChR-Ab Seronegative			
	Efgartigimod (N=65)		Placebo (N=64)		Efgartigimod (N=19)		Placebo (N=19)	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Cycle 1								
Actual $C1_B$	65	9.0 (0.31)	64	8.6 (0.27)	19	9.7 (0.72)	19	9.8 (0.58)
Week 4	63	−4.6 (0.40)	60	−1.8 (0.31)	17	−4.2 (0.82)	19	−2.7 (0.54)
Cycle 2								
Actual $C2_B$	51	9.9 (0.44)	43	9.1 (0.36)	12	9.8 (0.89)	14	10.6 (0.98)
Week 4	47	−5.1 (0.55)	42	−1.1 (0.29)	12	−4.5 (1.17)	13	−4.2 (1.47)

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Table 14.2.1.9.1
Abbreviations: AChR-Ab=anti-acetylcholine receptor antibody; Cn_B=baseline of cycle number; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set
Note: Only the first 2 cycles are shown due to the low number of patients with more than 2 cycles.

Table 27 – Percentage of patients with a minimum improvement of 2 to 5 points from cycle baseline at week 4 in MG-ADL total score in study ARGX-113-1704 (mITT analysis set)

Cycle	MG-ADL Total Score Change Criterion	% Meeting MG-ADL Total Score Change Criteria at Week 4 During the Cycle			
		AChR-Ab Seropositive		AChR-Ab Seronegative	
		Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod (N=19)	Placebo (N=19)
1	MG-ADL reduction ≥2	77.8	48.3	76.5	68.4
	MG-ADL reduction ≥3	73.0	36.7	64.7	47.4
	MG-ADL reduction ≥4	63.5	23.3	52.9	42.1
	MG-ADL reduction ≥5	55.6	11.7	41.2	26.3
2	MG-ADL reduction ≥2	80.9	33.3	75.0	53.8
	MG-ADL reduction ≥3	74.5	19.0	75.0	46.2
	MG-ADL reduction ≥4	63.8	11.9	50.0	38.5
	MG-ADL reduction ≥5	57.4	7.1	41.7	30.8

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Table 14.2.1.10.2
AChR-Ab=anti-acetylcholine receptor antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat

MGC:

In an MMRM analysis, the LS mean (SE) change in the MGC score at week 4 in the AChR-Ab seropositive population was −8.913 (0.974) in the efgartigimod group compared to −2.871 (1.007) in the placebo group (nominal p<0.0001). The LS mean (SE) change in the MGC score in the overall patient population (−9.231 [0.878] in the efgartigimod group compared to −4.497 [0.885] in the placebo group) were consistent with the improvements seen in the AChR-Ab seropositive population.

MG-QoL15r

In the AChR-Ab seropositive population during C1, patients in the efgartigimod group had greater reduction (improvements) in the MG-QoL15r total score compared with placebo, with LS mean differences >5 points at weeks 3, 4, and 5 (nominal p<0.0001) calculated from the MMRM analysis.

The difference in the change in the MG-QoL15r total score between the efgartigimod and placebo groups at week 4 is 5 points in favour of efgartigimod. The pooled SD for the population is 5.31. The effect size, calculated as the difference between groups/SD, is 0.94.

In the overall population during C1, the between-group LS mean differences in the efgartigimod group compared to placebo was >4 points at weeks 3, 4, and 5 (nominal p<0.0001).

MG-ADL Responder Onset and Duration:

Among cycle 1 MG-ADL responders, the duration of responder status was 6–7 weeks in 14 (32%) of 44 patients, 8–11 weeks in ten (23%) patients, and 12 weeks or more in 15 (34%) patients (Table 28).

Table 28 – MG-ADL responder onset and duration in the AChR-Ab seropositive population during cycle 1 (mITT analysis set)

	Efgartigimod (N=65)
MG-ADL responders, n (%)	44 (67.7)
Not MG-ADL responders, n (%)	21 (32.3)
MG-ADL onset of response in C1 MG-ADL responders, n (%)	
Week 1	23 (52.3)
Week 2	14 (31.8)
Week 3	4 (9.1)
Week 4	3 (6.8)
MG-ADL duration of response in C1 MG-ADL responders, n (%)	
≥4 weeks	44 (100)
≥6 weeks	39 (88.6)
≥8 weeks	25 (56.8)
≥12 weeks	15 (34.1)
≥18 weeks	8 (18.2)

Source: Section 14, Table 14.2.1.20.1
AChR-Ab=acetylcholine receptor antibody; C1=cycle 1; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set

Minimum Point Improvement in the MG-ADL Total Score:

The percentages of patients in the AChR-Ab seropositive population with increasing thresholds of reduction in MG-ADL total score at weeks 4 and 5 are presented in the Figure below.

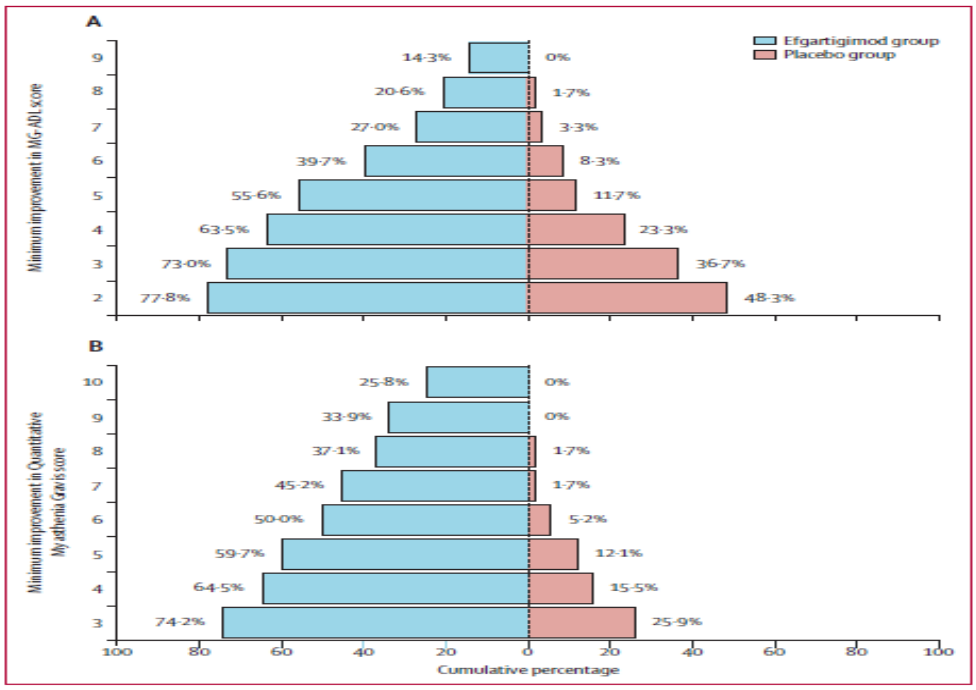


Figure 3: **Minimum point improvement in MG-ADL (A) and Quantitative Myasthenia Gravis (B) score in cycle 1, in acetylcholine receptor antibody-positive patients**
Minimum improvements 1 week after the last infusion of cycle 1 (week 4). MG-ADL=Myasthenia Gravis Activities of Daily Living.

Minimal Symptom Expression:

The MSE is characterised by an MG-ADL total score of 0 or 1. In the AChR-Ab seropositive population, an MG-ADL total score of 0 or 1 was observed anytime during C1 in 26 (40% patients in the efgartigimod group compared to 7 (11.1%) patients in the placebo group. An MG-ADL score of 0 or 1 was reported in 22.3% of patients in the efgartigimod group compared to 3.3% of patients in the placebo group at week 4 of C1 (Figure 18).

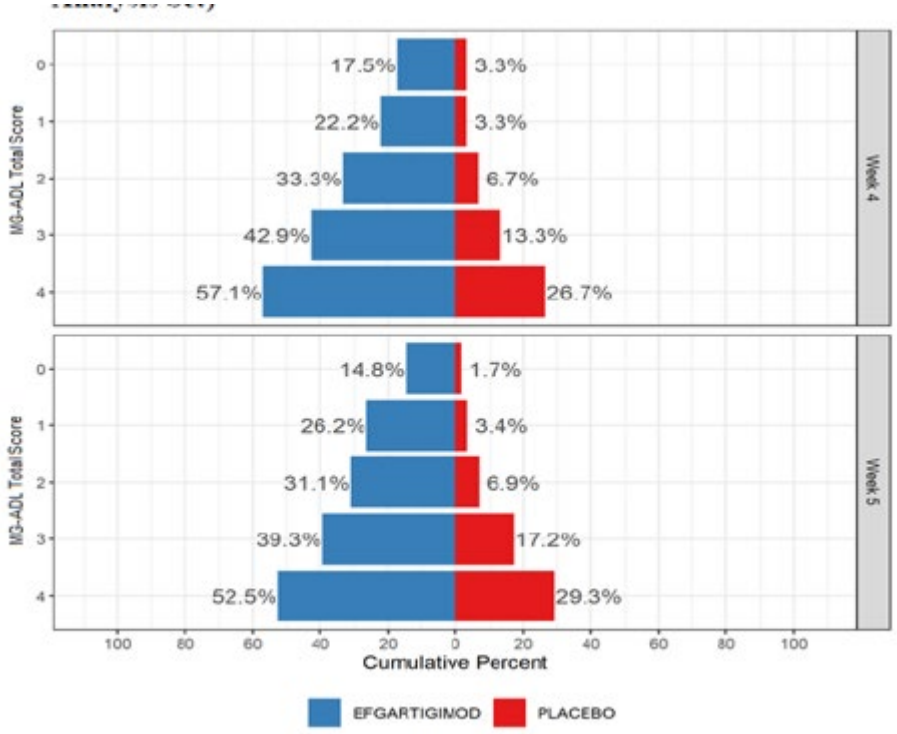


Figure 18 – Percentage of patients with MG-ADL total score actual values in the AChR-Ab seropositive population at week 4 and week 5 of cycle 1 (mITT analysis set)

MG-ADL Responders in Cycle 2: In patients who received a second cycle (ie, needed retreatment), 29 (90.6%) patients in the efgartigimod group were MG-ADL responders compared to 2 (33.3%) patients in the placebo group.

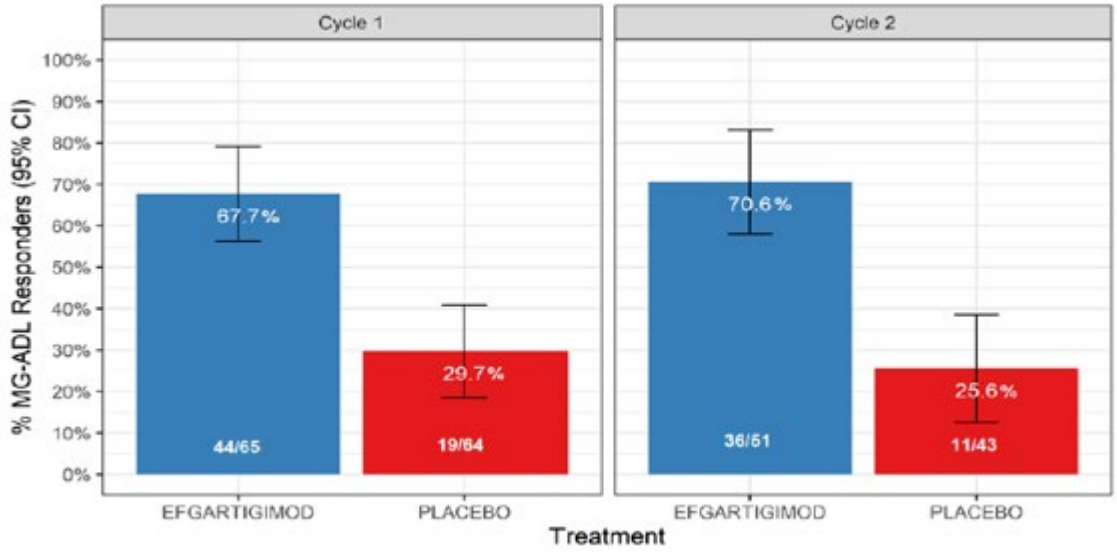


Figure 19 – Percentage of MG-ADL responders during cycle 1 and cycle 2 in the AChR-Ab seropositive population (mITT analysis set)

- **Ancillary analyses**

AChR-Ab seronegative population

In the AChR-Ab seronegative population during C1,

- 13 (68.4%) patients in the efgartigimod group and 12 (63.2%) patients in the placebo group were MG-ADL responders
- 10 (52.6%) patients in the efgartigimod group and 7 (36.8%) patients in the placebo group were QMG responders
- 9 (47.4%) patients in the efgartigimod group and 4 (21.1%) patients in the placebo group were both an MG-ADL responder and a QMG responder
- MSE (MG-ADL total score of 0 or 1) was observed in 6 (31.6%) patients in the efgartigimod group compared to 3 (15.8%) patients in the placebo group in C1.
- Mean change for MG-ADL total score was -4.2 for efgartigimod, -2.7 for placebo

In study ARGX-113-1704, 3 patients were randomized as AChR-Ab seronegative based on central laboratory results at screening; however, their medical history data indicated an AChR-Ab seropositive result. A sensitivity analysis was performed for patients who were AChR-Ab seronegative according to historical reports (or for whom no historical information was available) and following central laboratory testing. In this subgroup, 12 (66.7%) patients in the efgartigimod group were MG-ADL responders compared to 11 (64.7%) patients in the placebo group.

Examination of Subgroups

The results of subgroup analyses on the percentage of MG-ADL responders in the efgartigimod and placebo groups are presented in Table 29 and Figure 20. The percentages of MG-ADL responders were analysed by AChR-Ab serostatus, race, concomitant gMG treatment, MG-ADL total score at baseline category, and the number of administered cycles.

Table 29 – MG-ADL responders during cycle 1 by subgroup in the overall population (mIIT analysis set)

	Efgartigimod (N=84) n (%)	Placebo (N=83) n / N (%)	Difference in Response (95% CI)
Japanese	3 (42.9)	3 (42.9)	0.0 (-51.8; 51.8)

NonJapanese	54 (70.1)	28 (36.8)	33.3 (18.4; 48.2)
Race			
Black or African American	3 (100)	1 (33.3)	66.7 (13.3; 100)
Asian	4 (44.4)	3 (42.9)	1.6 (-47.4; 50.6)
White	47 (68.1)	26 (36.1)	32.0 (16.4; 47.6)
Concomitant gMG treatment			
NSID	33 (67.3)	19 (38.8)	28.6 (9.6; 47.5)
Non-NSID	24 (68.6)	12 (35.3)	33.3 (11.0; 55.5)
AChR-Ab Status			
Seropositive	44 (67.7)	19 (29.7)	38.0 (22.1; 54.0)
Seronegative	13 (68.4)	12 (63.2)	5.3 (-24.9; 35.4)
Age group			
18 to <65 years	49 (67.1)	30 (43.5)	23.6 (7.7; 39.5)
≥65 years	8 (72.7)	1 (7.1)	65.6 (36.0; 95.2)
Sex			
Female	44 (69.8)	23 (41.8)	28.0 (10.7; 45.3)
Male	13 (61.9)	8 (28.6)	33.3 (6.7; 60.0)
Region			
United States	20 (80.0)	5 (33.3)	46.7 (18.1; 75.2)
Japan	3 (37.5)	3 (42.9)	-5.4 (-55.0; 44.3)
Rest of World	34 (66.7)	23 (37.7)	29.0 (11.2; 46.7)
MG-ADL category at baseline			
5-7	11 (55.0)	9 (40.9)	14.1 (-15.87; 44.05)
8-9	22 (71.0)	10 (29.4)	41.6 (19.42; 63.69)
≥10	24 (72.7)	12 (44.4)	28.3 (4.15; 52.41)
Number of cycles			
1 cycle	18 (85.7)	18 (69.2)	16.5 (-6.73; 39.69)
2 cycles	33 (58.9)	12 (22.2)	36.7 (19.71; 53.71)
3 cycles	6 (85.7)	1 (33.3)	52.4 (-6.93; 100)

Source: Section 14, Tables 14.2.1.5.3 and 14.2.1.6.2
AChR-Ab=acetylcholine receptor antibody; CI=confidence interval; gMG=generalized myasthenia gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat; n=number of patients for

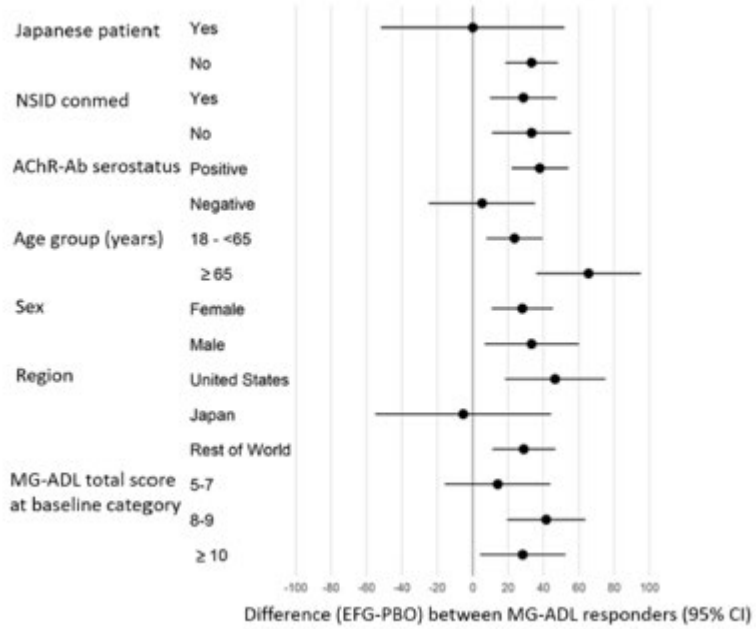


Figure 20 – MG-ADL responders during cycle 1 by subgroup for the overall population (mITT analysis set)

Table 30 – Demographics and baseline disease characteristics of MG-ADL responders during cycle 1 in the AChR-Ab seropositive population in study ARGX-113-1704 (mITT analysis set)

	Efgartigimod (N=65) n (%)	Placebo (N=64) n (%)	Difference in Response (95% CI)	Odds Ratio (95% Wald CI)
Race				
Black or African American	1 (100)	1 (33.3)	66.7 (13.3; 100)	Not calculable
Asian	2 (28.6)	1 (25.0)	3.6 (−50.5; 57.6)	1.20 (0.07; 19.63)
White	38 (70.4)	16 (28.6)	41.8 (24.8; 58.8)	5.94 (2.61; 13.52)
Concomitant gMG treatment				
NSID	25 (65.8)	11 (29.7)	36.1 (15.0; 57.1)	4.55 (1.72; 12.02)
Non-NSID	19 (70.4)	8 (29.6)	40.7 (16.4; 65.1)	5.64 (1.75; 18.14)
Age group				
18 to <65 years	38 (66.7)	19 (37.3)	29.4 (11.4; 47.5)	3.37 (1.53; 7.43)
≥65 years	6 (75.0)	0	75.0 (45.0; 100)	Not calculable
Sex				
Female	31 (67.4)	13 (32.5)	34.9 (15.0; 54.7)	4.29 (1.74; 10.60)
Male	13 (68.4)	6 (25.0)	43.4 (16.3; 70.6)	6.50 (1.71; 24.77)
Region				
United States	13 (86.7)	3 (27.3)	59.4 (28.0; 90.8)	17.33 (2.36; 127.34)
Japan	1 (16.7)	1 (25.0)	−8.3 (−60.2; 43.5)	0.60 (0.03; 13.58)
Rest of World	30 (68.2)	15 (30.6)	37.6 (18.7; 56.4)	4.86 (2.02;, 11.69)
MG-ADL category at baseline				
5-7	8 (50.0)	6 (33.3)	16.7 (−16.1; 49.4)	2.00 (0.50; 8.00)
8-9	18 (72.0)	7 (24.1)	47.9 (24.4; 71.4)	8.08 (2.39; 27.34)
≥10	18 (75.0)	6 (35.3)	39.7 (11.1; 68.3)	5.50 (1.42; 21.38)
Number of cycles				
1 cycle	12 (85.7)	13 (61.9)	23.8 (−3.9; 51.5)	3.69 (0.65, 20.97)
2 cycles	26 (59.1)	6 (14.3)	44.8 (26.8; 62.8)	8.67 (3.02, 24.83)
3 cycles	6 (85.7)	0	85.7 (59.8; 100)	Not calculable
Europe-EurAsia Region				
EEA	15 (60.0)	7 (25.9)	34.1 (8.7; 59.4)	4.29 (1.32, 13.88)
Europe	21 (63.6)	11 (33.3)	30.3 (7.3; 53.3)	3.50 (1.27, 9.64)
EurAsia	8 (80.0)	4 (28.6)	51.4 (17.2; 85.7)	10.00 (1.44; 69.26)
All	29 (67.4)	15 (31.9)	35.5 (16.2; 54.9)	4.42 (1.82; 10.71)

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Tables 14.2.1.5.1, 14.2.1.6.1, and 128.1
AChR-Ab=acetylcholine receptor antibody; CI=confidence interval; gMG=generalized myasthenia gravis; EEA=European Economic Area; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; NSID=nonsteroidal immunosuppressive drug
Note: The denominator for the percentage calculations is the total number of subjects per treatment and strata in the mITT analysis set.
Note: Definitions for the Europe-EurAsia regional analysis are:

- EEA – Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland.
- Europe – Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Serbia.
- EurAsia – Russia and Georgia.
- All – all countries in the Europe and EurAsia subgroups.

In the AChR-Ab seropositive population, 45 (69.2%) patients in the efgartigimod group had a history of thymectomy compared to 30 (46.9%) patients in the placebo group. A *post hoc* analysis was performed to assess the proportion of MG-ADL responders in patients with and without a history of thymectomy during C1.

In all AChR-Ab seropositive patients, regardless of treatment group, without a history of thymectomy, 28 (52%) were MG-ADL responders during C1. In patients with a thymectomy, 35 (47%) patients were

MG-ADL responders, representing a 5% difference in treatment effect in favour of patients without thymectomy.

In patients without a history of thymectomy 17 (85%) patients were MG-ADL responders in the efgartigimod group compared to 11 (32%) in the placebo group, which is a treatment effect of 53%.

In patients with a history of thymectomy, 27 (60%) patients were MG-ADL responders in the efgartigimod group compared to 8 (27%) patients in the placebo group, which is a treatment effect of 33%.

- **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 31 - Summary of Efficacy for trial ARGX-113-1704

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness			
Study identifier	Study Number: ARGX-113-1704 EudraCT Number: 2018-002132-25 NCT Number: 03669588		
Design	Randomized, multicenter, double-blind, placebo-controlled, efficacy, safety and tolerability study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks (8-week treatment cycles: comprising of 3-week treatment period and a 5-week follow-up period; and intertreatment cycles of variable length depending on the patient's clinical response 2 weeks (screening period)
Hypothesis	Superiority		
Treatments groups	Efgartigimod alfa		efgartigimod IV 10 mg/kg intravenously administered as a 1-hour infusion every 7 days (q7d) for 4 infusions
	Placebo		Placebo intravenously administered as a 1-hour infusion q7d for 4 infusions
Endpoints and definitions	Primary endpoint		The % of patients who, after the first cycle (C_1), had a reduction of at least 2 points on the MG-ADL total score (compared to baseline of the first cycle [$C1_B$]) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of efgartigimod alfa in AChR-Ab seropositive population

	Secondary endpoint	1	Percentage of patients who, after the first treatment cycle, have a decrease of at least 3 points on the total QMG score (compared to C_{1B}) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion in AChR-Ab seropositive patients
	Secondary endpoint	2	Percentage of patients who, after the first treatment cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the efgartigimod alfa group in the overall population (AChR Ab seropositive and AChR Ab seronegative patients)
	Secondary endpoint	3	Percentage of time that patients have a clinically meaning full improved (CMI) in MG-ADL total score compared to study entry baseline (SEB) during the study (up to and including day 126) in AChR Ab seropositive patients
	Secondary endpoint	4	Time from week 4 to qualify for retreatment (ie, the patient has <2-point reduction in the MG-ADL total score and MG-ADL total score of ≥5 points with >50% of the total score attributed to nonocular symptoms) in the AChR Ab seropositive population
	Secondary endpoint	5	Percentage of patients who, after the first treatment cycle, have a decrease of at least 2 points on the MG-ADL total score (compared to C_{1B}) for at least 4 consecutive weeks with the first of these decreases occurring at the latest after 1 or maximum 2 infusions of efgartigimod alfa (early MG ADL responders) in the AChR Ab seropositive patients. In practice, visit week 2 is the last visit the onset of response can start to be considered an early responder, even in case of a missed infusion.
Database lock eCRF data	13 May 2020		

<u>Results and Analysis</u>

Analysis description	**Primary endpoint of primary analysis: MG-ADL Responders in AChR-Ab seropositive Population**			
Analysis population and time point description	mITT analysis set, during C_1			
Primary endpoint	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**

Descriptive statistics and estimate variability	Number of subject	65	64	
	n (%)	44 (67.7%)	19 (29.7%)	
	Odds Ratio (95% CI)			4.951 (2.213, 11.528) P<0.0001
Analysis description	**Secondary key endpoints: QMG responders in the AChR-Ab seropositive population.**			
Analysis population and time point description	mITT analysis set, during C_1			
Secondary key endpoint 1 Descriptive statistics and estimate variability	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**
	Number of subject	65	64	
	n (%)	41 (63.1%)	9 (14.1%)	
	Odds Ratio (95% CI)			10.842 (4.179, 31.200) P<0.0001
Analysis description	**Secondary key endpoints: MG-ADL responders in overall population.**			
Analysis population and time point description	mITT analysis set, during C_1			
Secondary key endpoint 2 Descriptive statistics and estimate variability	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**
	Number of subject	84	83	
	n (%)	57 (67.9%)	31 (37.3%)	
	Odds Ratio (95% CI)			3.699 (1.854, 7.578) P<0.0001
Analysis description	**Secondary key endpoints: Percentage of time that patients have a CMI in MG-ADL total score compared to SEB in AChR Ab seropositive patients.**			
Analysis population and time point description	mITT analysis set; Up to and including day 126			
Secondary key endpoint 3 Descriptive statistics and estimate variability	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**
				Difference / *P-value*
	Number of subject	65	64	
	LS mean (SE)	48.714 (6.163)	26.649 (6.316)	22.065 (5.616) / 0.0001
	95% CI	(36.517; 60.912)	(14.148; 39.151)	(10.949; 33.181)

Analysis description	**Secondary key endpoints: Median Time to Qualify for Retreatment in the AChR-Ab Seropositive Population.**			
Analysis population and time point description	mITT analysis set			
Secondary key endpoint 4 Descriptive statistics and estimate variability	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**
	Number of subject	65	64	
	Days	35	8	
	Median (95% CI)	(29.0, 43.0)	(1.0, 30.0)	P = 0.2604
Analysis description	**Secondary key endpoints: Early MG-ADL responders in the AChR-Ab seropositive population.**			
Analysis population and time point description	mITT analysis set, during C_1			
Secondary key endpoint 5 Descriptive statistics and estimate variability	**Treatment group**	**Efgartigimod alfa**	**Placebo**	**Efgartigimod alfa vs. placebo**
	Number of subject	65	64	
	n (%)	37 (56.9)	16 (25.0)	
Notes	This endpoint was not tested because a statistically significant difference between the efgartigimod and placebo groups was not attained in the previous endpoint in the hierarchy			

2.6.5.3. Clinical studies in special populations

Table 32 – Age group categories in studies ARGX-113-1602, ARGX-113-1704, and ARGX-113-1705

Age Group (Years)	Efgartigimod (N=96) n (%)	Placebo-Efgartigimod (N=66) n (%)	Overall (N=162) n (%)
<65	81 (84.4)	56 (84.8)	137 (84.6)
≥65	15 (15.6)	10 (15.2)	25 (15.4)
≥65-<75	12 (12.5)	6 (9.1)	18 (11.1)
≥75-<85	3 (3.1)	4 (6.1)	7 (4.3)
≥85	0	0	0

Source: Module 5.3.5.3, ARGX-113-MG-ISE – EMA output: Table 48.1

Patients with renal or hepatic impairment were not excluded from the pivotal study. Although allowed as per study inclusion and exclusion criteria, no patients with hepatic impairment were enrolled in any efgartigimod clinical study. Meanwhile, 52 and 6 patients were classified as patients with mild (eGFR ≥60 to <90 mL/min/1.73 m^2) and moderate (eGFR ≥30 to <60 mL/min/1.73 m^2) renal impairment,

respectively. No patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) were included. To date, clinical data for patients with moderate or severe renal impairment is limited. Data in patients with mild renal impairment showed there was no impact on the overall safety profile. The effects of hepatic or renal impairment on the pharmacokinetics of efgartigimod has not been formally studied.

No paediatric patients have been treated with efgartigimod. There is missing information with regard to the elderly patients as only 8 patients above 65 years were treated with efgartigimod in study ARGX-113-1704. Subjects had an age range of 19-81 years at baseline.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analyses of data from these 3 studies were also performed to further confirm the treatment effect of efgartigimod in patients with gMG, and they encompassed 3 pooling blocks. The primary endpoints were different in the 3 clinical studies. Each of the 3 clinical studies included an evaluation of the efficacy scales MG-ADL and QMG, and, as such, the integrated efficacy analyses compared changes in each scale to the cycle baseline measurement. No hypothesis testing was performed, and all analyses provided are descriptive.

Tables 33 and 34 provide patient disposition and duration of cycles in pool 2.

Table 33 – Overview of pooled analysis for efficacy assessments

Pooling Block	Clinical Studies	Patient Population	Treatment Groups/ Cohorts	Endpoints Analyzed and Treatment Cycles
1	ARGX-113-1602 ARGX-113-1704	AChR-Ab seropositive patients	• placebo • efgartigimod	For Cycle 1:[a] • Change in MG-ADL • Change in QMG • Categorical change in MG-ADL • Categorical change in QMG • Minimum MG-ADL and QMG score • Maximum drop in MG-ADL and QMG • Change in total IgG and IgG subtypes
2	ARGX-113-1602 ARGX-113-1704 ARGX-113-1705 (Interim analysis 3)	All patients with gMG treated with efgartigimod • AChR-Ab seropositive • AChR-Ab seronegative • Overall patient population	• efgartigimod • placebo-efgartigimod • total efgartigimod	For each Cycle: • Change in MG-ADL • Change in QMG • Change in total IgG, IgG subtypes, and anti-AChR antibodies • Categorical change in MG-ADL • Categorical change in QMG • Minimum MG-ADL and QMG score during cycle • Maximum drop in MG-ADL and QMG
3	ARGX-113-1602 ARGX-113-1704 ARGX-113-1705 (Interim analysis 3)	All patients with gMG who participated in studies • AChR-Ab seropositive patients • Overall patient population	• placebo • efgartigimod • placebo-efgartigimod • efgartigimod-efgartigimod	Over time (regardless of cycle) • Change in MG-ADL • Change in QMG • Change in total IgG and anti-AChR antibodies

AChR-Ab=anti-acetylcholine receptor antibody; AEs=adverse events; ECG=electrocardiogram; IgG=immunoglobulin G; MG=Myasthenia Gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living; PB1=pooling block 1; QMG=Quantitative Myasthenia Gravis; SAEs=serious adverse events

[a] Because of differences in the scheduled assessments, the definition of MG-ADL responder in study ARGX-113-1602 is different from the one in the main study ARGX-113-1704. Therefore, there is no MG-ADL responder analysis in PB1.

Table 34 – Patient disposition – pooling block 2

Patient Population Analysis Set	Efgartigimod (n)	Placebo-Efgartigimod (n)	Total Efgartigimod (n)
AChR-Ab seropositive population			
All randomized patients set	77	54[a]	131
mITT analysis set	77	48	125
Overall population			
All randomized patients set	96[b]	72[a]	168
mITT analysis set	96	66[c]	162

Sources: Module 5.3.5.3, ARGX-113-9012-ISE, Table 14.1.1.2.1.1 and Table 14.1.1.2.1.2
AChR-Ab=anti-acetylcholine receptor antibody; mITT=modified intent-to-treat; n=number of patients
Note: The planned treatment as randomized/received is shown.
[a] Includes 6 placebo-treated patients who rolled over from study ARGX-113-1704 to the open-label study but had not received open-label efgartigimod. These patients are excluded from the mITT analysis set.
[b] Randomized patients from ARGX-113-1704 (efgartigimod n=84) and ARGX-113-1602 (efgartigimod n=12).
[c] Patients in the placebo-efgartigimod cohort (n=66) in open-label study ARGX-113-1705 (interim analysis 3).

Table 35 – Duration of cycles in PB2 – all patients (AChR-Ab seropositive and seronegative) (safety analysis set)

	Patients With At Least X Cycles		Cohort of Patients With a Maximum of X Cycles			
		Individual Cycle Duration (days)[a]		Duration of Follow-up (days)[b]		Average Cycle Duration (days)
Cycle X	N (%)	Median (min, max)	N (%)	Mean (SD)	Median[c] (min, max)	Based on Median Follow-up[c]
1	162 (100)	72.0 (42, 616)	24 (14.8)	221.1 (203.30)	78.5 (42, 616)	78.5
2	138 (85.2)	71.0 (15, 470)	11 (6.8)	334.1 (169.37)	368.0 (116, 608)	184.0
3	127 (78.4)	60.0 (15, 354)	20 (12.3)	361.3 (168.07)	367.0 (114, 714)	122.3
4	107 (66.0)	57.0 (4, 300)	17 (10.5)	388.2 (140.21)	370.0 (213, 666)	92.5
5	90 (55.6)	52.5 (35, 156)	5 (3.1)	392.0 (118.25)	418.0 (269, 560)	83.6
6	85 (52.5)	52.0 (5, 183)	18 (11.1)	428.3 (87.44)	389.0 (281, 617)	64.8
7	67 (41.4)	54.0 (14, 138)	10 (6.2)	484.7 (75.06)	525.0 (351, 551)	75.0
8	57 (35.2)	50.0 (1, 93)	20 (12.3)	468.3 (117.76)	413.5 (349, 713)	51.7
9	37 (22.8)	50.0 (5, 97)	14 (8.6)	519.3 (70.16)	507.0 (407, 678)	56.3
10	23 (14.2)	42.0 (5, 57)	14 (8.6)	536.9 (80.01)	513.5 (469, 721)	51.4
11	9 (5.6)	50.0 (5, 58)	3 (1.9)	529.7 (0.58)	530.0 (529, 530)	48.2
12	6 (3.7)	46.5 (7, 50)	3 (1.9)	646.3 (29.19)	631.0 (628, 680)	52.6
13	3 (1.9)	50.0 (29, 50)	1 (0.6)	672.0 (NA)	672.0 (NA, NA)	51.7
14	2 (1.2)	11.5 (8, 15)	2 (1.2)	686.5 (0.71)	686.5 (686, 687)	49.0

Sources: Module 5.3.5.3, ARGX-113-9011-ISS, Tables 14.1.3.2.1, 14.1.1.2.3, and 14.1.1.2.7
max=maximum; min=minimum; N=number of patients; NA=not available; PB2=pooling block 2; SD=standard deviation; X=number of cycles
[a] The individual cycle duration is the median number of days from the first infusion of a cycle to the first infusion of the next cycle or the data cutoff date, whichever comes first; therefore, the duration of an individual patient's last cycle may appear shorter.
[b] The duration of follow-up is the number of days from the first infusion to the end of the observation period (ie, the end of the study or the data cutoff date, whichever comes first).
[c] The average cycle duration is calculated as the median duration of follow-up divided by the number of cycles.

Week 3 is the timepoint selected for the summary of PB2 due to limited visits scheduled in the open-label study, ARGX-113-1705; unlike in the antecedent study, ARGX-113-1704, patients in the open-label study did not have a scheduled visit at weeks 4, 5, and 6. In AChR-Ab seropositive patients, marked MG-ADL improvements (≥3-, ≥5-, ≥7-point reductions from cycle baseline) were achieved in efgartigimod-treated patients (81.6%, 60.8%, 37.6%, respectively) in C1. Similar MG-ADL improvements were seen in all cycles; more than 50% of patients had ≥5-point reductions from cycle baseline in MG-ADL score.

A summary of the mean change from cycle baseline in QMG total score at week 3 is provided in Table 36 for the different cycle cohorts of AChR-Ab seropositive patients. In AChR-Ab seropositive patients, QMG improvements (≥3- through to ≥9-point reductions from cycle baseline) were achieved in efgartigimod-treated patients (83.2% through to 32.0% of patients, respectively) in C1. Similar QMG improvements were seen in all cycles.

Table 36 – Changes from cycle baseline in MG-ADL total score at week 3 by cycle cohort in AChR-Ab seropositive patients treated with efgartigimod – PB2 (mITT analysis set)

MG-ADL Total Score Timepoint	Cohort Receiving at Least n Cycles								
	≥1 (N=125)	≥2 (N=106)	≥3 (N=96)	≥4 (N=83)	≥5 (N=70)	≥6 (N=67)	≥7 (N=51)	≥8 (N=43)	≥9 (N=27)
Cycle 1 baseline									
N	125	106	96	83	70	67	51	43	27
Mean (SE)	8.9 (0.23)	9.0 (0.25)	8.9 (0.27)	8.9 (0.29)	9.0 (0.33)	8.9 (0.33)	9.0 (0.39)	8.9 (0.41)	8.6 (0.44)
Cycle 1 / Week 3 change from cycle baseline									
N	124	105	95	83	70	67	51	43	27
Mean (SE)	-4.0 (0.27)	-3.9 (0.29)	-4.0 (0.32)	-4.2 (0.34)	-4.2 (0.38)	-4.2 (0.38)	-4.6 (0.44)	-4.4 (0.47)	-4.4 (0.63)
Cycle 2 baseline									
N		106	96	83	70	67	51	43	27
Mean (SE)		9.6 (0.29)	9.6 (0.31)	9.7 (0.34)	9.9 (0.38)	9.8 (0.40)	10.0 (0.47)	10.1 (0.51)	9.9 (0.64)
Cycle 2 / Week 3 change from cycle baseline									
N		104	96	83	70	67	51	43	27
Mean (SE)		-4.8 (0.32)	-4.9 (0.34)	-5.1 (0.36)	-5.3 (0.40)	-5.3 (0.41)	-5.7 (0.47)	-5.7 (0.54)	-5.9 (0.69)
Cycle 3 baseline									
N			96	83	70	67	51	43	27
Mean (SE)			9.8 (0.32)	9.9 (0.36)	10.0 (0.41)	9.9 (0.42)	10.1 (0.50)	10.1 (0.54)	9.7 (0.67)
Cycle 3 / Week 3 change from cycle baseline									
N			93	80	67	65	49	41	26
Mean (SE)			-5.2 (0.37)	-5.6 (0.39)	-5.7 (0.43)	-5.8 (0.43)	-6.4 (0.48)	-6.6 (0.53)	-6.6 (0.64)
Cycle 4 baseline									
N				83	70	67	51	43	27
Mean (SE)				10.2 (0.39)	10.3 (0.44)	10.2 (0.46)	10.5 (0.54)	10.5 (0.58)	10.2 (0.70)
Cycle 4 / Week 3 change from cycle baseline									
N				80	69	66	50	42	26
Mean (SE)				-5.7 (0.41)	-6.1 (0.43)	-6.0 (0.43)	-6.5 (0.51)	-6.6 (0.57)	-6.8 (0.68)
Cycle 5 baseline									
N					70	67	51	43	27
Mean (SE)					10.5 (0.44)	10.4 (0.45)	10.7 (0.54)	10.8 (0.58)	10.3 (0.71)
Cycle 5 / Week 3 change from cycle baseline									
N					70	67	51	43	27
Mean (SE)					-5.8 (0.43)	-5.8 (0.43)	-6.2 (0.51)	-6.0 (0.57)	-6.4 (0.78)
Cycle 6 baseline									
N						67	51	43	27
Mean (SE)						10.4 (0.43)	10.7 (0.50)	10.7 (0.55)	10.4 (0.68)
Cycle 6 / Week 3 change from cycle baseline									
N						62	51	43	27
Mean (SE)						-6.1 (0.49)	-6.2 (0.52)	-6.3 (0.59)	-6.4 (0.80)
Cycle 7 baseline									
N							51	43	27
Mean (SE)							10.7 (0.54)	10.6 (0.59)	10.4 (0.75)
Cycle 7 / Week 3 change from cycle baseline									
N							50	43	27
Mean (SE)							-6.6 (0.51)	-6.7 (0.56)	-7.0 (0.75)
Cycle 8 baseline									
N								43	27
Mean (SE)								10.9 (0.51)	10.4 (0.64)
Cycle 8 / Week 3 change from cycle baseline									
N								37	27
Mean (SE)								-6.6 (0.63)	-6.3 (0.75)
Cycle 9 baseline									
N									27
Mean (SE)									11.0 (0.62)
Cycle 9 / Week 3 change from cycle baseline									
N									21
Mean (SE)									-7.6 (0.75)

Source: Module 5.3.5.3, ARGX-113-9012-ISE, Table 14.2.1.2.1.1

AChR-Ab=anti-acetylcholine receptor antibody; mITT=modified intent-to-treat; MG-ADL=Myasthenia Gravis Activities of Daily Living; N=total number of patients; n=number of evaluable patients at timepoint; PB2=pooling block 2; SE=standard error

Note: "Cycle n baseline" is the last available value prior to or on the day of first efgartigimod administration in cycle n.

Table 37 – Changes from cycle baseline in QMG total score at week 3 by cycle cohort in AChR-Ab seropositive patients treated with efgartigimod – PB2 (mITT analysis set)

	Cohort Receiving at Least n Cycles								
QMG Total Score Timepoint	≥ 1 (N=125)	≥ 2 (N=106)	≥ 3 (N=96)	≥ 4 (N=83)	≥ 5 (N=70)	≥ 6 (N=67)	≥ 7 (N=51)	≥ 8 (N=43)	≥ 9 (N=27)
Cycle 1 baseline									
n	125	106	96	83	70	67	51	43	27
Mean (SE)	15.8 (0.45)	16.0 (0.48)	16.3 (0.50)	16.3 (0.55)	16.8 (0.59)	16.8 (0.62)	17.4 (0.68)	17.7 (0.70)	17.5 (0.99)
Cycle 1 / Week 3 change from cycle baseline									
n	123	104	94	83	70	67	51	43	27
Mean (SE)	-4.8 (0.40)	-4.7 (0.42)	-4.9 (0.46)	-5.2 (0.49)	-5.1 (0.55)	-5.1 (0.56)	-5.3 (0.66)	-5.4 (0.75)	-5.9 (1.09)
Cycle 2 baseline									
n		106	96	83	70	67	51	43	27
Mean (SE)		15.8 (0.54)	16.0 (0.57)	15.9 (0.64)	16.9 (0.68)	16.8 (0.70)	17.3 (0.81)	17.7 (0.91)	16.9 (1.29)
Cycle 2 / Week 3 change from cycle baseline									
n		100	93	81	69	66	50	42	27
Mean (SE)		-4.6 (0.43)	-4.7 (0.46)	-4.7 (0.51)	-5.0 (0.52)	-5.0 (0.52)	-5.2 (0.60)	-5.5 (0.71)	-5.7 (0.89)
Cycle 3 baseline									
n			96	83	70	67	51	43	27
Mean (SE)			15.4 (0.58)	15.3 (0.64)	15.7 (0.71)	15.6 (0.73)	16.6 (0.83)	16.9 (0.88)	16.3 (1.23)
Cycle 3 / Week 3 change from cycle baseline									
n			87	75	64	62	48	40	26
Mean (SE)			-4.4 (0.49)	-4.7 (0.54)	-4.7 (0.60)	-4.7 (0.62)	-5.2 (0.73)	-5.6 (0.83)	-6.0 (1.17)
Cycle 4 baseline									
n				83	70	67	51	43	27
Mean (SE)				15.7 (0.67)	16.2 (0.75)	16.1 (0.78)	17.1 (0.89)	17.2 (0.97)	16.5 (1.35)
Cycle 4 / Week 3 change from cycle baseline									
n				72	63	60	47	40	26
Mean (SE)				-4.7 (0.49)	-5.0 (0.53)	-4.8 (0.52)	-5.3 (0.61)	-5.6 (0.68)	-5.8 (0.87)
Cycle 5 baseline									
n					70	67	51	43	27
Mean (SE)					16.0 (0.70)	15.9 (0.72)	16.7 (0.81)	17.1 (0.90)	16.3 (1.24)
Cycle 5 / Week 3 change from cycle baseline									
n					56	54	41	36	23
Mean (SE)					-4.7 (0.64)	-4.8 (0.65)	-5.4 (0.79)	-5.8 (0.86)	-6.7 (1.19)
Cycle 6 baseline									
n						67	51	43	27
Mean (SE)						15.6 (0.73)	16.4 (0.87)	16.6 (0.99)	15.7 (1.41)
Cycle 6 / Week 3 change from cycle baseline									
n						46	39	34	22
Mean (SE)						-4.7 (0.66)	-4.8 (0.74)	-5.0 (0.83)	-5.7 (1.13)
Cycle 7 baseline									
n							51	43	27
Mean (SE)							16.7 (0.91)	16.7 (0.99)	15.7 (1.40)
Cycle 7 / Week 3 change from cycle baseline									
n							34	30	20
Mean (SE)							-5.7 (0.73)	-5.7 (0.77)	-5.9 (1.03)
Cycle 8 baseline									
n								43	27
Mean (SE)								15.9 (1.05)	14.9 (1.45)
Cycle 8 / Week 3 change from cycle baseline									
n								16	15
Mean (SE)								-4.4 (1.06)	-4.4 (1.13)
Cycle 9 baseline									
n									27
Mean (SE)									14.9 (1.39)
Cycle 9 / Week 3 change from cycle baseline									
n									11
Mean (SE)									-6.1 (1.26)

Source: Module 5.3.5.3, ARGX-113-9012-ISE, Table 14.2.2.2.1.1
AChR-Ab=anti-acetylcholine receptor antibody; mITT=modified intent-to-treat; QMG=Quantitative Myasthenia Gravis; N=total number of patients; n=number of evaluable patients at timepoint; PB2=pooling block 2; SE=standard error
Note: "Cycle n baseline" is the last available value prior to or on the day of first efgartigimod administration in cycle n.

A summary of the mean change from cycle baseline in MG-ADL total score at week 3 in PB2 and study ARGX-113-1704 is provided in Table 38 for AChR-Ab seronegative patients.

Table 38 – Changes from cycle baseline in MG-ADL total score at week 3 in AChR-Ab seronegative patients – PB2 and study ARGX-114-1704

	Pooling Block 2							
	Efgartigimod (N=19)		Placebo-Efgartigimod (N=18)		Total Efgartigimod (N=37)		ARGX-113-1704 Efgartigimod (N=19)	
MG-ADL total score Timepoint	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Cycle 1 Baseline MG-ADL	19	9.7 (0.72)	18	10.7 (0.87)	37	10.2 (0.56)	19	9.7 (0.72)
Cycle 1 / Week 3	18	-2.8 (0.64)	18	-4.5 (1.06)	36	-3.7 (0.63)	18	-2.8 (0.64)
Cycle 2 Baseline MG-ADL	15	10.0 (0.72)	17	11.1 (0.79)	32	10.6 (0.54)	12	9.8 (0.89)
Cycle 2 / Week 3	15	-5.1 (1.05)	17	-4.8 (0.94)	32	-4.9 (0.69)	11	-4.5 (1.19)
Cycle 3 Baseline MG-ADL	15	11.1 (0.80)	16	11.1 (0.77)	31	11.1 (0.55)	NA	NA
Cycle 3 / Week 3	15	-6.0 (1.04)	15	-5.3 (1.01)	30	-5.6 (0.72)	NA	NA
Cycle 4 Baseline MG-ADL	12	11.3 (1.01)	12	10.7 (0.86)	24	11.0 (0.65)	NA	NA
Cycle 4 / Week 3	11	-5.4 (1.25)	12	-4.3 (1.07)	23	-4.8 (0.81)	NA	NA
Cycle 5 Baseline MG-ADL	9	11.7 (1.08)	11	11.3 (0.84)	20	11.5 (0.65)	NA	NA
Cycle 5 / Week 3	9	-7.1 (1.45)	11	-6.0 (1.15)	20	-6.5 (0.89)	NA	NA
Cycle 6 Baseline MG-ADL	8	12.0 (1.30)	10	11.4 (1.00)	18	11.7 (0.78)	NA	NA
Cycle 6 / Week 3	8	-7.1 (1.46)	10	-5.0 (0.86)	18	-5.9 (0.82)	NA	NA
Cycle 7 Baseline MG-ADL	7	11.9 (1.40)	9	11.1 (0.99)	16	11.4 (0.81)	NA	NA
Cycle 7 / Week 3	7	-7.0 (1.79)	9	-5.7 (1.03)	16	-6.3 (0.95)	NA	NA
Cycle 8 Baseline MG-ADL	5	9.8 (1.46)	9	10.9 (1.05)	14	10.5 (0.83)	NA	NA
Cycle 8 / Week 3	5	-6.0 (2.02)	7	-6.6 (0.84)	12	-6.3 (0.92)	NA	NA

2.6.5.5. Supportive studies

Study ARGX-113-1705 (Open-Label Extension of Study ARGX-113-1704)

A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness

Study ARGX-113-1705 is an ongoing, open-label, single-arm, multicenter, 2-part, 3-year extension of the completed, pivotal, phase 3 study ARGX-113-1704. The study is conducted in 2 sequential parts: Part A (1 year) and Part B, which was added to ensure patients could have continued access to efgartigimod. Data from the 01 February 2021 cut-off (third interim analysis) are provided in this application.

At the EoS visit for Study ARGX-113-1704, patients were offered the option to roll over into a long-term, single-arm, open-label follow-on trial (ARGX-113-1705) where they are treated with ARGX-113 (10 mg/kg of body weight) on an "as needed basis". Patients who need re-treatment but cannot complete a Treatment Cycle within the time frame of the ARGX-113-1704 trial, could roll over immediately to the follow-on trial to receive treatment with ARGX-113.

Patients who discontinued early from trial ARGX-113-1704, or from randomised treatment for rescue or pregnancy reasons or for an (S)AE that might jeopardize the safety of the patient were not offered the option to roll over in the follow-on trial.

The primary objective of this study was to assess long-term safety and tolerability of efgartigimod in AChR-Ab seropositive patients. The secondary objective was to evaluate the long-term safety and tolerability of efgartigimod IV 10 mg/kg in the overall population.

As of 01 February 2021, of the 167 patients enrolled in the double-blinded antecedent study ARGX-113-1704, 151 patients had rolled over into this study, and 139 patients have received at least 1 dose of efgartigimod. Of these, 73 patients had previously received efgartigimod ("efgartigimod-efgartigimod cohort"), and 66 patients had previously received placebo ("placebo-efgartigimod cohort") in study ARGX-113-1704. Overall, 29 (20.9%) patients have discontinued treatment, and 110 (79.1%) patients were still ongoing. The maximum number of completed cycles was 10.

In total, 139 patients started C1, and 4 patients started C11 (C11 was ongoing at time of data cut-off). Median cycle durations were 64.0 days for C1, 57.0 days for C2, and 50 to 54 days for each of the cycles C3 to C10. The mean (SD) duration of treatment and follow-up in this interim analysis was 363.0 (113.65) days (approximately 52 weeks).

The majority of patients were AChR-Ab seropositive (76.3%). Of the 73 patients in the efgartigimod-efgartigimod cohort, 58 patients were AChR-Ab seropositive and 15 patients were AChR-Ab seronegative. Of the 66 patients in the placebo-efgartigimod cohort, 48 patients were AChR-Ab seropositive, and 18 patients were AChR-Ab seronegative.

The median age was 45.0 years and most patients were White (87.8%) and female (71.2%). The median time since diagnosis of gMG was 7.10 years, the median MG-ADL total score was 10.0, and the median QMG total score was 16.0.

Exploratory endpoints included mean change in total MG-ADL or QMG scores from cycle baseline to Week 3 in AChR-Ab seropositive patients and overall population.

In the AChR-Ab seropositive population, the mean change from cycle baseline in the MG-ADL total score was numerically greater in the efgartigimod-efgartigimod cohort than in the placebo-efgartigimod cohort for the first 9 cycles. Similar results were observed in the overall population.

For all cycles, greater than 90% and 50% of patients in the AChR-Ab seropositive population had a minimum point improvement from cycle baseline in the MG-ADL total score of 2 and 5points, respectively. Similar results were observed in the overall population.

QMG scores were collected only during Part A of study ARGX-113-1705 (ie, maximum 7 cycles).

MG-ADL total score - mean change from cycle baseline at Week 3 in the AChR-Ab seropositive population

Treatment group	**EFG-EFG (N=58)**		**PBO-EFG (N=48)**		**Total EFG (N=106)**	
	n	**Mean (SE)**	**n**	**Mean (SE)**	**n**	**Mean (SE)**
Cycle 1	56	-6.0 (0.49)	47	-4.0 (0.41)	103	-5.1 (0.34)
Cycle 2	51	-6.2 (0.55)	44	-4.4 (0.43)	95	-5.4 (0.37)
Cycle 3	44	-6.4 (0.52)	41	-4.3 (0.49)	85	-5.4 (0.38)
Cycle 4	39	-7.0 (0.62)	32	-4.7 (0.58)	71	-6.0 (0.45)
Cycle 5	34	-7.1 (0.61)	27	-4.6 (0.57)	61	-6.0 (0.45)
Cycle 6	26	-7.0 (0.80)	23	-4.7 (0.74)	49	-5.9 (0.57)

Cycle 7	19	-8.1 (0.73)	16	-5.5 (0.84)	35	-6.9 (0.59)
Cycle 8	8	-8.9 (0.95)	9	-6.1 (1.35)	17	-7.4 (0.89)
Cycle 9	6	-8.7 (1.43)	3	-6.7 (2.40)	9	-8.0 (1.20)
MG-ADL total score - mean change from cycle baseline at Week 3 in the overall population						
Treatment group	**EFG-EFG (N=73)**		**PBO-EFG (N=66)**		**Total EFG (N=139)**	
	n	**Mean (SE)**	**n**	**Mean (SE)**	**n**	**Mean (SE)**
Cycle 1	71	-6.1 (0.45)	65	-4.1 (0.41)	136	-5.1 (0.32)
Cycle 2	64	-6.1 (0.49)	61	-4.5 (0.40)	125	-5.3 (0.32)
Cycle 3	54	-6.6 (0.49)	56	-4.6 (0.45)	110	-5.6 (0.34)
Cycle 4	47	-7.0 (0.56)	44	-4.5 (0.51)	91	-5.8 (0.40)
Cycle 5	41	-7.0 (0.58)	38	-5.0 (0.53)	79	-6.1 (0.41)
Cycle 6	31	-6.9 (0.73)	33	-4.8 (0.57)	64	-5.8 (0.48)
Cycle 7	23	-7.6 (0.75)	25	-5.6 (0.64)	48	-6.5 (0.51)
Cycle 8	10	-8.4 (0.97)	16	-6.3 (0.82)	26	-7.1 (0.65)
Cycle 9	6	-8.7 (1.43)	7	-6.1 (1.52)	13	-7.3 (1.07)

Study ARGX-113-1602

A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness

Completed study ARGX-113-1602 is a Phase 2, randomised, double-blind, placebo-controlled, multicenter study in patients with gMG. Overall, 24 patients were planned to be randomised in 1:1 ratio to receive either efgartigimod IV 10 mg/kg or matched placebo intravenously infused over 2 hours q7d for 4 infusions concomitantly with their existing gMG therapies. The maximum amount of efgartigimod IV administered to patients who weighed ≥120 kg was 1200 mg in a single infusion.

The study included a screening period of up to 15 days, a 3-week TP, and an 8-week follow-up period.

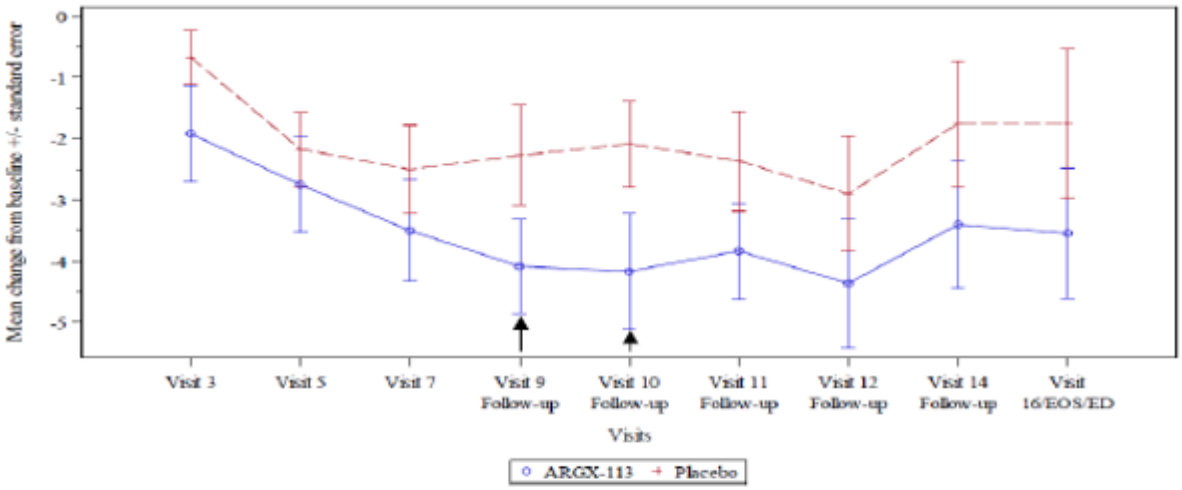
Patients continued to receive individualised concomitant gMG therapies (eg, NSIDs, steroids, and acetylcholinesterase inhibitors), and changes were not permitted even if used for indications other than gMG. Rescue therapy was permitted if the patient deteriorated based on the Investigator's overall clinical assessment, and patients who required rescue therapy were discontinued from the study.

The primary objective was to evaluate the safety and tolerability of efgartigimod. Secondary objectives were to:

- Evaluate the clinical effect of efgartigimod using MG-ADL score, QMG score, MGC score
- Evaluate the impact of efgartigimod on quality of life using the MG-QoL15r (revised version)
- Investigate the PK of efgartigimod
- Assess PD markers (eg, total immunoglobulin G [IgG] and subtypes, anti-AChR antibodies)
- Evaluate the immunogenicity of efgartigimod

Of the 24 enrolled patients, 12 were randomised to efgartigimod IV 10 mg/kg and 12 to matched placebo. All patients completed the TP with a minimum of 2 weeks follow-up. One (8.3%) patient in the efgartigimod treatment group discontinued before the end of the follow-up period due to lack of efficacy.

All patients in the study were AChR-Ab seropositive. The majority of patients were female (62.5%) and Caucasian (91.7%). Median age was 56.5 years in the efgartigimod group and 46.0 years in the placebo group. Compared with the placebo group, a higher proportion of patients in the efgartigimod group were receiving corticosteroids or immunosuppressants: 8 (66.7%) and 9 (75.0%), respectively, in the efgartigimod group compared with 5 (41.7%) and 3 (25.0%), respectively, in the placebo group.



Source: Figure 14.2.1.1, Section 14; corresponding data Table 14.2.1.1.
Abbreviations: ED = Early Discontinuation; EOS = End-of-Study; FU = Follow-up; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; stderr = standard error.
Note: Arrow shows statistically significant difference between ARGX-113 and placebo.
Note: Visit 3 = Day 8, Visit 5 = Day 15, Visit 7 = Day 22, Visit 9 (Week 1 FU) = Day 29, Visit 10 (Week 2 FU) = Day 36, Visit 11 (Week 3 FU) = Day 43, Visit 12 (Week 4 FU) = Day 50, Visit 14 (Week 6 FU) = Day 64, Visit 16 (Week 8 FU EOS/ED) = Day 78.
Note: Doses administered at Day 1 (Visit 1), Day 8 (Visit 3), Day 15 (Visit 5), and Day 22 (Visit 7).

Figure 20 – Evolution of Mean MG-ADL change from baseline – full analysis set

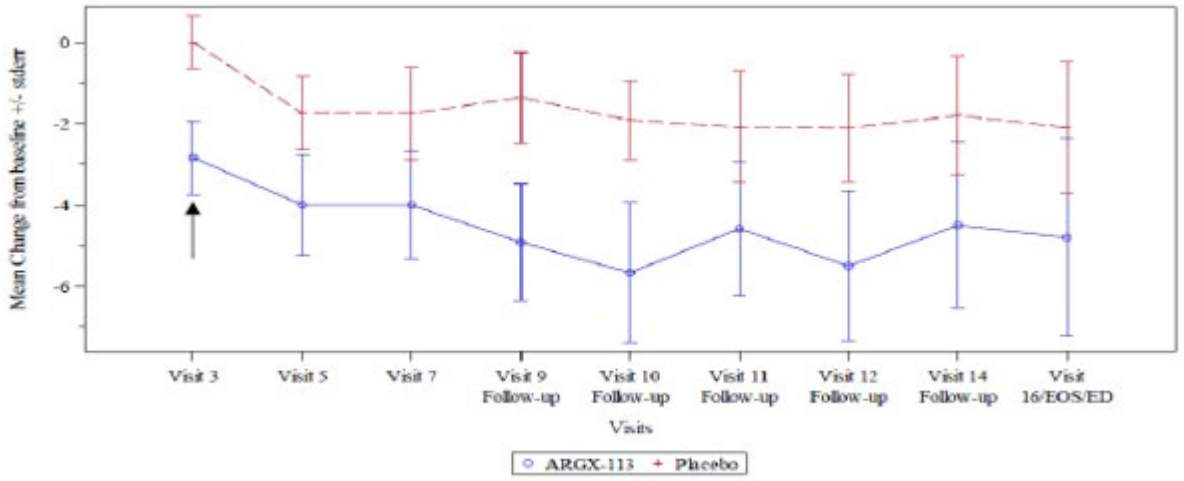


Figure 21 – Evolution of Mean QMG change from baseline – full analysis set

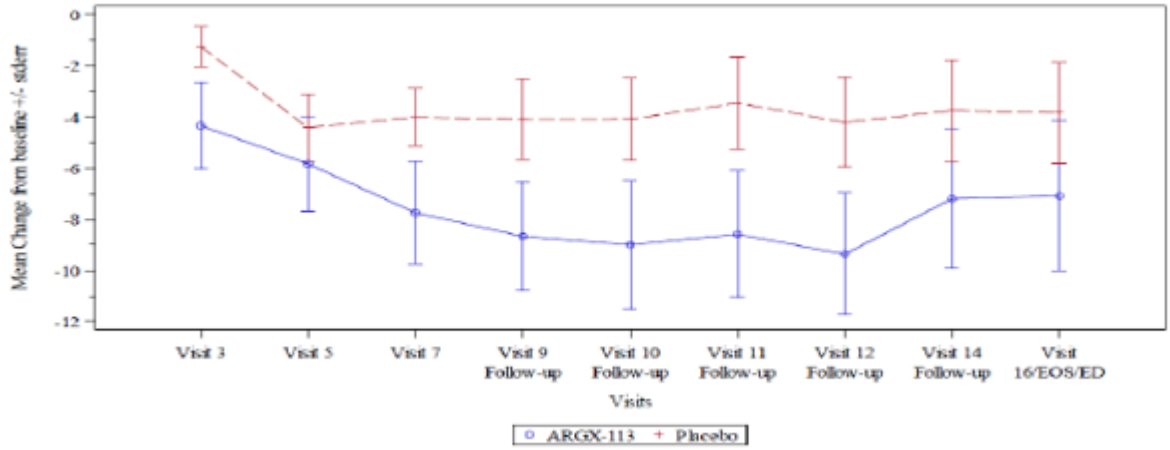


Figure 22 – Evolution of mean MGC change from baseline – full analysis set

2.6.6. Discussion on clinical efficacy

Efgartigimod, a neonatal Fc receptor (FcRn) antagonist, is a human IgG1 antibody (Ab) Fc-fragment, a natural ligand of FcRn that has been engineered for increased affinity to FcRn. Efgartigimod blocks FcRn, outcompeting endogenous IgG binding, preventing its recycling and resulting in increased IgG degradation.

The main evidence for demonstration of the efficacy of Vyvgart (efgartigimod) in the intended indication is based on data from one 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) is 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 is limited to analyses of MG-ADL changes (different definition and timing from primary endpoint in pivotal study). Additional supportive data from a Phase II study (ARGX-113-1602) and pooled analysis across Phase 2-3 trials was also submitted.

The initial proposed indication for efgartigimod has been modified to include "add-on to standard therapy for the treatment of adult patients with generalized Myasthenia Gravis who are anti-acetylcholine receptor (AChR) antibody positive" due to the lack of data about the inclusion of AChR-Ab seronegative patients.

The recommended dose schedule is 10 mg/kg (as a 1-hour intravenous infusion) to be administered in cycles of once weekly infusions for 4 weeks. Information about appropriate product administration and storage conditions are reflected in the SmPC. In the pivotal trial, the total dose per IMP infusion was capped at 1200 mg for patients with body weight ≥120 kg.

Design and conduct of clinical studies

The pivotal trial is a multicenter, multinational, randomised, double-blind, placebo-controlled, parallel group confirmatory trial. The study consisted of screening (2 weeks), randomised controlled (up to 26 weeks), and safety and disease severity follow up (30 to 182 days) periods. The randomised controlled period consisted of an initial 8-week treatment cycle where all randomised patients are treated with efgartigimod (3-week treatment period and a 5-week follow-up period) and a re-treatment part where patients could be re-treated with efgartigimod on an "as needed basis". The time between treatment cycles is based on the duration of the treatment effect and may vary from patient to patient and for each patient from cycle to cycle (patient-tailored approach). 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. The study was overseen by sponsor-appointed Data Safety Monitoring Board (DSMB) and a central laboratory was used for laboratory evaluations including AChR-Ab serotype. The overall study design is considered acceptable by CHMP. However, it is acknowledged that the length of follow up is a limitation, and treatment details and enrolled population will be discussed further.

The trial duration of 26 weeks (plus 2-week screening period) is considered sufficient for the demonstration of short-term efficacy. As MG is a chronic, fluctuant condition, long-term efficacy data will be also required. In this regard, Study 1705 currently ongoing will provide this information. This study has been included in the RMP has a Category 3 study in order to evaluate the long-term safety and tolerability of efgartigimod administered to patients with gMG and to collect additional safety data to supplement that from the randomized placebo-controlled study ARGX-113-1704

Eligible subjects were randomised in a 1:1 ratio to receive either efgartigimod or placebo in addition to their ongoing treatment for gMG. Subjects were stratified according to AChR-Ab status (seropositive or seronegative; 20% of AChR-Ab seronegative patients maximum), background SoC therapy (nonsteroidal immunosuppressive drugs/NSIDs or not NSIDs), and Japanese or non-Japanese.

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, some limitations are acknowledged.

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).

Both newly diagnosed and previously treated patients with suboptimal response were enrolled, and they continued to receive concomitant gMG therapies if they met "stable" definitions (eg, NSIDs, steroids, and AChE inhibitors) before screening and throughout the trial.. Patients were excluded if they had received rituximab or eculizumab in the 6 months before screening, undergone thymectomy within 3 months, had intravenous immunoglobulin or plasma exchange within 1 month of screening. It should be highlighted that conducting a placebo-controlled trial despite available approved therapies could raise some concerns, however, as nonsteroidal immunosuppressive drugs and steroids were allowed as background therapies, the CHMP considered that this approach is acceptable.

Efgartigimod alfa may decrease concentrations of compounds that bind to the human FcRn, i.e., immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc

domain of the IgG subclass. As such, patients who need chronic plasmapheresis, PE, IVIg or monoclonal antibodies for controlling symptoms were not allowed in the study.

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 any active infection (e.g. active hepatitis B, were seropositive for hepatitis C, seropositive for HIV with low CD4 count) or any major episode of infection that required hospitalisation or injectable antimicrobial therapy in the last 8 weeks prior to screening, with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, fluoroquinolones, beta-blockers, etc.), and patients who had a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders (unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before screening) were excluded from the pivotal study and were not studied with efgartigimod. Patients who received a vaccination within the last 4 weeks prior to screening or were pregnant were excluded and relevant warnings have been inserted in SmPC. Laboratory exclusion criteria were very limited and patients with renal/hepatic function impairment were allowed in the study however, no patients with hepatic impairment were included and therefore there is no clinical experience with treatment with efgartigimod in patients with hepatic impairment (please refer to Clinical Pharmacology section for further discussion on dose adjustment in patients with hepatic impairment).

It would have been expected that the selection criteria also included serologic diagnosis (specific antibodies) as they are widely considered highly specific for the diagnosis of MG and confirmative of the condition[10,11,12]. AChR-/MuSK antibody serotypes were tested at screening and their presence/absence was one of the stratification factors. It was planned the recruitment of a subset of AChR antibody seronegative patients (up to 20% of recruited patients). This is relevant because there are no approved therapies for this subset of patients. Patients positive to MuSK R antibodies or negative to AChR/MuSK R were qualified as seronegative patients.

Anti-AchR antibodies are primarily of the IgG1 and IgG3 isotypes, MuSK Abs are predominantly of the IgG4 isotype. A third antibody (to low-density lipoprotein-related receptor protein 4; Lrp4) has been described, which is predominantly of the IgG1 isotype. Therefore, both seropositive and seronegative patients would be candidates to be treated with efgartigimod since its mechanism of action results in the reduction of total IgG and IgG subtypes.

Efgartigimod was administered on top of background therapy. It may increase the acceptability of the study and the recruitment but also results in increased heterogeneity of the population recruited. Also, the fact that patients were on concomitant treatment may make it more difficult for the interpretation of clinical results and the assessment of the effect of an additional therapeutic agent. However, CHMP considered that this did not hinder the strength of the efficacy results.

In the pivotal Trial ARGX-113-1704, a total of 167 patients were randomised to efgartigimod (n=84) and placebo (n=83) on top of their background therapy at 56 international sites (in 15 countries). 66 patients (51%) were enrolled in Europe and the population is considered as representative of patients in EU. AChR-Ab status was seropositive in 129 (77.2%) patients (mITT set) and seronegative in 38 (22.8%) patients. At entry, the majority of patients were concomitantly treated with anticholinesterases (83%), steroids (76%), and other immunosuppressants (61%, NSIDs) and no changes were allowed during the study. Majority (93.4%) had at least 2 prior therapies, and 77.2% of patients had at least 3 prior therapies. Approximately 29% (48) patients had not received NSIDs as a prior medication for MG. The

[10] Gilhus NE et al. Nat Rev Dis Primers 2019; 5: 30
[11] Nguyen, T., Phan CL, Supsupin E, Sheikh K. Neurol Clin 2020 Aug;38(3):577-590.
[12] Gilhus NE. N Engl J Med 2016;375:2570-81

most frequently reported MGFA class at screening was Class III in 96 (57.4%) patients followed by Class II in 65 (39%) patients, indicative of a symptomatic patient population with moderate to mild weakness affecting muscles other than the ocular muscles. The mean baseline MG-ADL (9.0) and QMG (15.9) scores demonstrate substantial disease burden despite ongoing generalised myasthenia gravis treatment. Overall, 152 (91.0%) patients completed treatment and 156 (93.4%) patients completed the study. The majority of patients who discontinued from treatment did so in C1; 5 (6%) patients in the efgartigimod group and 10 (12%) patients in the placebo group. Treatment compliance was very high. There were slight imbalances between treatment arms in terms of demographics and disease characteristics, most probably due to small number of patients overall and 3 different stratification criteria on AChR-Ab status, SoC and Japanese origin. However, there were no notable differences among the treatment groups which would be expected to favour treatment with efgartigimod.

Seronegative patients showed worse baseline scores than seropositive patients. Mean MG-ADL score was 9 vs 8.3, respectively, with 50% of seronegative group showing MG-ADL scores ≥10 vs 30% of seropositive group. Mean QMG score was 16.5 vs 15.6, respectively; the figures for MGC score were 19.2 vs 18.4, respectively.

This pivotal study was primarily aimed to evaluate the short-term effect of efgartigimod (during the first cycle) on seropositive gMG patients. Also, the secondary objectives are mainly focused in this subset.

The evaluation of efficacy was based mainly on MG-ADL (subjective assessment of MG symptoms by the patient) and QMG (quantitative evaluation of relevant muscle groups by the physician) scales. Several definitions of responders and related secondary or exploratory endpoints were used. MGC and MG-QoL15r were also used as specific scales but not as primary or key secondary endpoints, they are considered as supportive at best. The selected endpoints are validated standard methods for evaluation of MG and have been previously used in several clinical studies in this condition. Of note, the primary objective was only evaluating the efficacy in the seropositive population.

The primary endpoint was the percentage of patients who, after the first cycle, had a reduction of at least 2 points on the MG-ADL total score (compared to baseline of the first cycle) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the investigational medicinal product in AChR-Ab seropositive population.

The usual primary efficacy endpoint in clinical trials in gMG condition is the change from baseline to efficacy time point in the total score on the MG-ADL scale. In Study 1704 the definition of responders includes those patients who achieve a clinically meaningful (decrease from baseline of ≥2 points), early (≤ 1 week after the last infusion) and durable (≥4 consecutive weeks) response on the MG ADL in Cycle 1. As the symptoms/signs associated with gMG are fluctuating, the choice of the primary endpoint is considered to be acceptable. It should also be read in conjunction with mean changes (absolute values) with respect to baseline values. The responder rates may also help establishing the relevance of the effect although dichotomic variables are less informative than continuous ones.

It was unclear why the primary endpoint is only focused on seropositive patients since a general indication was sought. It would have been expected that the primary analysis would have been performed in the whole population with appropriate subgroup analyses. No specific analysis of response in seronegative patients was planned in the secondary endpoints analysis hierarchy. In fact, they were only considered in one of the secondary endpoints as part of the Overall population. Since the mechanism of action is not specifically targeted to Ab against ACh receptor it would not be expected that anti-AChR positive patients respond differently than anti-Musk positive or other autoantibodies positive patients. However, this may well be the case for anti-MuSK R Ab. The reduction experienced by IgG4 subtype (the type related to anti-MuSK Ab) was of lower magnitude than that showed by other subtypes and close to placebo curve (see Pharmacokinetics and Pharmacodynamics section). Therefore, since the primary

endpoint focused only on seropositive patients the indication was amended such as only seropositive patients are included.

Efficacy data and additional analyses

The primary endpoint was met in study ARGX-113-1704, meaning symptomatic relief on MG-ADL (less functional disability of MG patients), during first treatment cycle in the AChR-Ab seropositive population (mITT set). In this population, the MG-ADL responder criterion was met in 44 (67.7%) patients in the efgartigimod group compared to 19 (29.7%) patients in the placebo group, with an OR (95% CI) of 4.95 (2.21;11.53) ($p<0.0001$; logistic regression testing). The results of sensitivity analysis of primary endpoint using data from PP population are consistent with the results in the mITT set. A 2-point reduction in MG-ADL total score can be considered as clinically meaningful and the data from exploratory analyses are considered supportive. The mean (95% CI) change from SEB 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. Patients achieved improvements of up to 10 points in MG-ADL total score during C1. The percentage of patients with increasing thresholds of MG-ADL improvement (≥2, ≥3, ≥4, ≥5, ≥6, ≥7, ≥8) at week 4 in C1 was higher in efgartigimod patients (77.8%, 73.0%, 63.5%, 55.6%, 39.7%, 27.0%, 20.6%, respectively) compared to placebo patients (48.3%, 36.7%, 23.3%, 11.7%, 8.3%, 3.3%, 1.7%, respectively) and was similar between 2 or 3 points cut-offs. Overall, efgartigimod treatment in comparison to placebo has demonstrated a statistically significant and clinically relevant efficacy in treatment of AChR-Ab seropositive population in study ARGX-113-1704, as rated by patients.

The first three secondary endpoints also showed a statistically significant and clinically relevant effect of efgartigimod in comparison to placebo.

QMG responders in the AChR-Ab seropositive population during C1 were significantly higher in efgartigimod group. The QMG responder criterion was met in 41 (63.1%) seropositive patients in the efgartigimod group compared to 9 (14.1%) seropositive patients in the placebo group during C1 and the OR (95% CI) is 10.84 (4.18; 31.20) ($p<0.0001$; logistic regression testing). A 3.5-point difference has been shown to correlate with clinically meaningful change. Clinical meaningfulness of a ≥3 points change versus ≥4 points cut-off could be seen as borderline, however, due to clear difference between study arms on this physician assessment with a high OR, the result is considered as clinically significant in the AChR-Ab seropositive population.

The percentage of MG-ADL responders in the overall population during C1 was the second secondary endpoint tested in the hierarchy and was the first endpoint in testing hierarchy including the overall population. The MG-ADL responder criterion was met in 57 (67.9%) patients in the efgartigimod group compared to 31 (37.3%) patients in the placebo group and the OR (95% CI) is 3.70 (1.85; 7.58) ($p<0.0001$; logistic regression testing). In seronegative subgroup, placebo and efgartigimod arms did not have noticeable difference, hence this difference on MG-ADL scale seems to be driven only by the AChR-Ab seropositive population.

The mean (SE) percentage of time AChR-Ab seropositive patients were reported to be showing a CMI was 48.714 (6.163) in the efgartigimod group compared to 26.649 (6.316) in the placebo group ($p=0.0001$). The median time to qualification for re-treatment was 8 days in the placebo group and 35 days in the efgartigimod group, and the difference between the groups was not statistically significant ($p=0.2604$). According to testing hierarchy, the testing stops after this endpoint and the other endpoints are considered as exploratory only.

Other scales of interest, MGC and MG-QoL15r, are also supportive of the efficacy of efgartigimod over placebo in the AChR-Ab seropositive population. The MGC score estimate at week 4 in the AChR-Ab seropositive population was −5.768 in the efgartigimod group compared to 0 in the placebo group. The

difference in the change in the MG-QoL15r total score between the efgartigimod and placebo groups at week 4 is 5 points in favour of efgartigimod. As reference, the 3-point reduction in the MGC (considered as clinically relevant) would correspond to a mean improvement in MG-QoL15 score by 12 points. For example, in a randomized trial comparing IVIg and plasmapheresis, both groups showed similar reduction in QMG scale and mean six- to nine-point improvements in MGQoL15 scores after treatment. The MGC change with efgartigimod is considered clinically relevant while detected QoL change is rather narrow.

The onset and duration of the MG-ADL response during C1 is an exploratory endpoint, however it is considered as informative for clinical practice. Of the 44 (67.7%) patients who were MG-ADL responders in C1, onset of response was week 1 for 23 (52.3%) patients and week 2 for 14 (31.8%) patients. The duration of response on the MG-ADL scale was ≥6 weeks in 39 (88.6%) responders and ≥8 weeks in 25 (56.8%) responders. The MG-ADL response rates in C2 were similar to those in C1. In general, the improvement in efgartigimod treated patients started at week 1 and reached maximum at week 4 for MG-ADL, QMG, MSC scales.

At week 4 in C2, the mean (95% CI) change from cycle baseline in MG-ADL total score was −5.1 (−6.24 to −4.01) points in the efgartigimod group and −1.1 (−1.70 to −0.54) points in the placebo group. These results support the continuum of effect in second cycle. However, beyond cycle 2, there were only 10 patients entering cycle 3 in the randomised trial period and maintenance of efficacy beyond 2 cycles is not shown for efgartigimod in randomised placebo-controlled studies.

Among 21 patients in the efgartigimod group who were not MG-ADL responders during cycle 1, 19 were retreated and seven (37%) of these were MG-ADL responders in cycle 2. Six (86%) of seven patients in the efgartigimod group who received a third cycle were MG-ADL responders (data from publication of phase 3 study). No data was submitted that would allow to identify some patients who might be late responders e.g. patients who did not benefit from C1 but needed a 2nd or 3rd cycle to achieve response. As efgartigimod has not been tested in MFGA class V patients and onset of response can be delayed (was observed within 2 weeks of initial infusion in 37/44 [84%] patients treated with efgartigimod alfa in the AChR Ab seropositive MG ADL responders) the clinicians should be careful not to use efgartigimod as bridging therapy or at the time of myasthenic exacerbations as rescue therapy. Treatment with efgartigimod alfa in patients with MGFA Class V (i.e. myasthenic crisis), defined as intubation with or without mechanical ventilation except in the setting of routine postoperative care, has not been studied. The sequence of therapy initiation between established therapies for MG crisis and efgartigimod alfa, and their potential interactions, should be considered (see section 4.5 of the SmPC).

Achieving minimal manifestation status is goal of treatment for MG patients in general. In the AChR-Ab seropositive population, an MG-ADL score of 0 or 1 was reported in 22.3% of patients in the efgartigimod group compared to 3.3% of patients in the placebo group at week 4 of C1. This is considered clinically relevant and supportive of the primary and key secondary endpoints.

The early onset of action and observed benefit in patients with or without previous NSID exposure suggest that efgartigimod might be used throughout disease continuum of patients with GMG. Acetylcholine receptor antibodies cause a net reduction of functional acetylcholine receptors at the postsynaptic membrane. However, patients with gMG also have increased acetylcholine receptor synthesis and repopulation, shown through mRNA and protein production, presumably as compensatory mechanisms. Because of this, the reduction of acetylcholine receptor antibodies by efgartigimod after one infusion could lead to a corresponding increase in acetylcholine receptors at the postsynaptic membrane and potentially account for the early onset of effect.

Nearly all patients (93.4%) included in the pivotal study had at least 2 prior therapies, and 77.2% of patients had at least 3 prior therapies. During the study, approximately 70% of efgartigimod-treated patients were receiving steroids and 60% were receiving NSIDs. They represent a heavily treated

population. The effect of efgartigimod on monotherapy has not been investigated andas such, Vyvgart is only indicated as an add-on to standard therapy. .

Among the ancillary analyses and subgroups, the AChR-Ab seronegative group is of particular interest. In this subgroup, there were 38 patients in total (19 in each treatment arm) and during C1 there was a similar number of MG-ADL responders in each treatment group, 13 (68.4%) patients in the efgartigimod group and 12 (63.2%) patients in the placebo group. The numbers for QMG responders and minimal symptom expression show a trend to favour efgartigimod treatment, however the numbers are too small to support a convincing treatment difference which was also not observed with MG-ADL responder analysis. There were only six patients with anti-MUSK antibodies, three in each treatment group, and all six were MG-ADL responders in cycle 1 regardless of treatment group they were assigned to.

Very high placebo response in AChR-Ab seronegative group was investigated in terms of any baseline differences to the AChR-Ab seropositive placebo population (disease severity, time since diagnosis, serotype according to central lab versus medical history, autoantibody levels, past and concomitant treatments used) despite the obvious limitations of any analysis on this subgroup due to study design. The AChR-Ab seronegative patients who received placebo were slightly younger (mean age 44.8 years vs 49.2 years), mostly female (78.9% vs 62.5%), with lower percentage of prior thymectomy for MG (31.6% vs 46.9%) and a shorter time since thymectomy (mean of 6.43 years vs 11.56 years), with higher mean MG-ADL total score (9.8 vs 8.6), with higher percentage of patients with a MG-ADL total score category of ≥10 (52.6% vs 26.6%), using higher percentage of NSIDs as concomitant gMG medication (73.7% vs 57.8%) Difference in AChR-Ab serotype according to central laboratory versus medical history (3 patients) was not an explanation and higher percentage of patients of Japanese origin (15.8% vs 6.3%) is not expected to shift the balance although could be a contributary factor. In conclusion, the reason for the higher MG-ADL placebo response in AChR-Ab seronegative patients in the placebo group remains unclear. There is no sound explanation for lack of difference in effect between treatment arms in seronegative population.

It is acknowledged that AChR-Ab seronegative gMG is a rare subset of an orphan disease, with few treatment options, and these patients are rarely included in clinical trials. Some AChR-Ab seronegative patients without known autoantibodies have been treated successfully with plasma exchange, supporting the IgG-mediated etiology of disease. Efgartigimod treatment is expected to reduce IgG autoantibodies similary among the various MG subtypes (maybe less with IgG4). There were 10 seronegative patients who were positive for MUSK (serotyping, n=6) or LRP4 (n=1, medical history) or AChR (n=3, medical history). They were equally distributed between active and placebo. Due to small numbers no interpretation can be made.

In summary, 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. The magnitude of change required to indicate an improvement or worsening of the condition is variable and depends on the severity of MG. The clinical profile of double seronegative patients might differ from AChR-Ab or MUSK-Ab seropositive patients, might be a milder course or might manifest as pure ocular MG more frequently, and the treatment responses might differ significantly from AChR-Ab seropositive patients. Although there is no clear evidence that efgartigimod reduces IgG autoantibodies differently among the various MG subtypes, the the primary endpoint was focused on the AChR-Ab seropositive population only. Due to lack of power to assess the efficacy AChR-Ab seronegative patients based on sample size considerations and the primary endpoint definition, heterogeneity resulting from inclusion of a broad AChR-Ab seronegative population, and no evidence of benefit for AChR-Ab seronegative patients on MG-ADL over placebo, the indication was limited to AChR Ab seropositive patients.

The MG-ADL responder analysis by subgroups showed two populations in which no effect is observed: Japanese/Asian population and seronegative patients, with a high placebo effect in both cases (Japanese patients: efgartigimod 42.9% vs. placebo 42.9%; seronegative patients: efgartigimod 68.4% vs. placebo 63.2%).

Two additional subgroups showed imbalanced responses: male patients and patients older than 65 years showed higher treatment effect than females and adult patients, respectively, but in these cases the reduced numbers of some subsets may have influenced the results.

With respect to long-term efficacy data, interim analysis results from Study ARGX-113-1705 (3-year extension, up to a maximum of 10 completed cycles by the current data cut-off date of 1 February 2021) and pooled analyses with Phase 2/3 data were available at the time of this report. Results from the interim analysis indicate a positive effect on the maintenance of the response to efgartigimod for AChR-Ab seropositive patients; with well-known caveats of open label design and withdrawal bias. The overall population showed similar trends. When patients who received placebo in the Study ARGX-113-1704 were treated with efgartigimod in Study ARGX-113-1705 an improvement similar to that showed by patients on active treatment in the previous study was observed. In patients previously treated with efgartigimod, the response was maintained.

Patients who were treated with efgartigimod in the pivotal trial showed a positive effect on the maintenance of the response to efgartigimod. This response was of lower magnitude in patients who received placebo in the pivotal trial than those treated with efgartigimod and in seronegative population with respect to seropositive patients. The main limitations are related to the low number of patients completing the treatment after the first cycles as these low numbers do not allow to achieve a solid conclusion.

2.6.7. Conclusions on the clinical efficacy

Evidence of the efficacy of Vyvgart (efgartigimod) in the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive, as an add-on to standard therapy, has been demonstrated.

Maintenance of the effect still remains to be confirmed by longer term data from the ongoing extension study.

There is no evidence to support a positive B/R on AChR seronegative patients and as such the approved indication is focused on seropositive patients.

The CHMP therefore considered that the available clinical efficacy data supports the use of Vyvgart in the approved indication.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The clinical safety database is based on two Phase 1 studies in adult subjects (ARGX-113-1501 and ARGX-113-1702), three Phase 2 and 3 clinical studies in adult patients with gMG (ARGX-113-1602, ARGX-113-1704 and ongoing study ARGX-113-1705) and one supportive study in adult patients with primary ITP (ARGX-113-1603). The safety database was grouped into three pooling blocks (PB1, PB2 and PB3).

- Pooling block 1 (PB1), based on double-blind, placebo-controlled studies in gMG (studies ARGX-113-1602 and cycle 1 of ARGX-113-1704). The objective of this pool was to evaluate the safety of efgartigimod compared to placebo in patients during C1.
- Pooling block 2 (PB2), based on all patients with gMG treated with efgartigimod (studies ARGX-113-1602, ARGX 113-1704, and data from ARGX-113-1705 up to the cut-off date of 01 February 2021). Data from studies ARGX-113-1602 and ARGX-113-1704 were pooled, and the data of the open-label extension study ARGX-113-1705 were combined with the preceding study ARGX-113-1704. This pooling was performed to maximize the amount of efgartigimod data in each cycle and to allow for analysis of outcomes as they evolved in patients who received at least the same number of cycles. This pooling of data allows for an evaluation of longitudinal safety data as well as groups of serial 3-month treatment intervals since initiating treatment with efgartigimod (i.e., months 0 to 3, 4 to 6, 10 to 12, 13 to 15, 16 to 18, and 19 to 21).
- Pooling block 3 (PB3), based on all patients with gMG or ITP who received efgartigimod in clinical studies up to 01 February 2021 (studies ARGX-113-1602, ARGX-113-1603, ARGX-113-1704 and data from ARGX-113-1705).

* Safety analysis of PB1 is based on the final data from ARGX-113-1602 and ARGX-113-1704. Safety analyses of PB2 and PB3 are based on data from the 01 February 2021 cut-off date.

Overall, a total of 252 subjects have been exposed to at least one dose of efgartigimod, as of the analysis cut-off date of 01 February 2021. The total number includes 60 healthy subjects, 162 patients with gMG and 30 patients with primary ITP. Of the 162 gMG patients exposed to efgartigimod IV 10 mg/kg, a total of 84 patients were treated with the proposed dosing regimen during the initial 28 weeks of the pivotal study and 139 patients entered into the extension study.

In the assessment of the safety of efgartigimod the two studies ARGX-113-1704 and ARGX-113-1705 as well as PB2 were used as the main clinical safety database. The two Phase 1 studies Study ARGX-113-1501 and Study ARGX-113-1702 as well as study ARGX-113-1603 in ITP patients were used as supportive safety database and were included where considered appropriate.

Studies ARGX-113-1704 and ARGX-113-1705

In study ARGX-113-1704, a total of 167 patients received at least 1 dose of efgartigimod (84 were assigned to the efgartigimod IV 10 mg/kg group and 83 were assigned to the placebo group). The mean (standard deviation [SD]) duration in the study (i.e., period starting from the first dose until the end of study) was comparable between the treatment groups. The mean (SD) duration of C1 was 94.4 (38.79) days in the efgartigimod group and 98.4 (46.11) days in the placebo group; C2 was 71.4 (9.85) days and 75.5 (14.50) days, respectively; and C3 was 53.7 (17.45) days and 62.0 (1.73) days, respectively.

After rolling over from the antecedent study ARGX-113-1704 to study ARGX-113-1705, 139 patients had received at least 1 dose of efgartigimod by the interim cut-off date of 01 February 2021. Of these patients, 73 patients received efgartigimod, and the remaining 66 patients received placebo in study ARGX-113-1704. Patients who received efgartigimod in the prior study, ARGX-113-1704, are labelled as "efgartigimod-efgartigimod cohort"; patients who received placebo are labeled as "placebo-efgartigimod cohort." The maximum number of cycles completed as of the 01 February 2021 database cut-off was 10.

Pooling Block 2: All Patients With gMG Who Received Efgartigimod Pool

PB2 includes data from all patients with gMG who received efgartigimod IV 10 mg/kg in studies ARGX-113-1602 and ARGX-113-1704 and data from study ARGX-113-1705 up to the data cut-off date of 01

February 2021. Only safety data observed/collected while patients were receiving efgartigimod are included in the PB2 safety analyses. Data observed while patients were receiving placebo are excluded. 162 patients received at least 1 dose of efgartigimod. A maximum of 14 cycles were started in patients. The mean (SD) duration of treatment combined with follow-up was 413.9 (170.26) days in the total efgartigimod group. The cumulative duration of treatment exposure was 183.6 total patient-years. Overall, the duration of treatment combined with follow-up was at least 6 months for 143 (88.3%) patients, at least 12 months for 118 (72.8%) patients, at least 18 to <24 months for 33 (20.4%) patients, and at least 24 to <30 months for 1 (0.6%) patient.

2.6.8.2. Adverse events

Analysis of Adverse Events

Studies in Patients with Generalised Myasthenia Gravis (Studies ARGX-113-1704 and ARGX-113-1705)

An overview of TEAEs in studies ARGX-113-1704 and ARGX-113-1705 is provided in Table 39.

Table 39 – Overview of treatment-emergent adverse events in studies ARGX-113-1704 and ARGX-113-1705 (safety analysis set)

	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall										
≥1 TEAE	65 (77.4)	252	70 (84.3)	270	61 (83.6)	267	51 (77.3)	294	112 (80.6)	561
≥1 SAE	4 (4.8)	4	7 (8.4)	10	14 (19.2)	25	7 (10.6)	10	21 (15.1)	35
≥1 TEAE of CTCAE severity ≥grade 3	9 (10.7)	10	8 (9.6)	12	15 (20.5)	38	11 (16.7)	19	26 (18.7)	57
≥1 AESI[a]	39 (46.4)	56	31 (37.3)	42	33 (45.2)	62	32 (48.5)	54	65 (46.8)	116
≥1 IRR event[b]	3 (3.6)	3	8 (9.6)	9	6 (8.2)	6	4 (6.1)	6	10 (7.2)	12
≥1 TEAE resulting in fatality	0	0	0	0	4 (5.5)	4	1 (1.5)	1	5 (3.6)	5
≥1 Treatment-related TEAE[c]	26 (31.0)	64	22 (26.5)	54	23 (31.5)	57	16 (24.2)	83	39 (28.1)	140
≥1 Procedure-related TEAE	1 (1.2)	1	0	0	4 (5.5)	4	1 (1.5)	1	5 (3.6)	5
≥1 Treatment-related SAE	1 (1.2)	1	0	0	0	0	0	0	0	0
≥1 TEAE for which IMP was discontinued	3 (3.6)	7	3 (3.6)	3	6 (8.2)	8	2 (3.0)	2	8 (5.8)	10

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 12.2.1, Table 41; Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 12.2.1, Table 26.
AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP= investigational medicinal product; IRR=infusion-related reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per treatment and per analysis period; SMQ=standardized MedDRA queries; SAE=serious adverse event; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: Efgartigimod-efgartigimod refers to the cohort of patients who received efgartigimod in the antecedent study ARGX-113-1704 and are receiving it in extension study ARGX-113-1705. Placebo-efgartigimod refers to the cohort of patients who received placebo in the antecedent study ARGX-113-1704 and are receiving efgartigimod in extension study ARGX-113-1705.
[a] An AESI was defined as any TEAE in the MedDRA SOC Infections and Infestations.
[b] IRRs were defined as adverse events within the SMQ (broad selection) for hypersensitivity, anaphylactic reaction, or extravasation events (excluding implants) and occurring within 48 h of an infusion, or within 2 days in case no start time was available.
[c] The causality of the event was determined by the investigator.

Pooling Block 2: All Patients with gMG who Received Efgartigimod Pool

The overview of all TEAEs that occurred in PB2, is presented in Table 40.

Table 40 – Overview of treatment-emergent adverse events reported in pooling block 2 (safety analysis set)

	Total Efgartigimod (N=162)		
	n (%)	m	PYFU
Overall			
≥1 TEAE	136 (84.0)	884	481.6
≥1 SAE	25 (15.4)	39	21.2
≥1 TEAE of CTCAE severity grade ≥3	32 (19.8)	67	36.5
≥1 Fatal TEAE	5 (3.1)	5	2.7
≥1 Related TEAE[a]	63 (38.9)	233	126.9
≥1 Related SAE[a]	1 (0.6)	1	0.5
≥1 TEAE leading to interruption of IMP	16 (9.9)	23	12.5
≥1 TEAE leading to discontinuation of IMP	11 (6.8)	17	9.3
≥1 AESI[b]	90 (55.6)	179	97.5
≥1 IRR[c]	13 (8.0)	16	8.7

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.1.1

AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IRR=infusion-related reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per treatment; PI=principal investigator; PYFU=event rates per 100 patient-years of follow-up; SAE=serious adverse event; SMQ=standardized MedDRA queries; TEAE=treatment-emergent adverse event.

[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 TEAE in the MedDRA SOC Infections and Infestations.

[c] IRRs were defined as adverse events within the SMQ (broad selection) for hypersensitivity, anaphylactic reaction, or extravasation events (excluding implants) and occurring within 48 h of an infusion, or within 2 days in case no start time was available.

The frequency of TEAEs and treatment-emergent AESIs observed in the total efgartigimod group generally decreased in subsequent cycles (Table 41).

Table 41 – Overview of treatment-emergent adverse events in pooling block 2 by cycle (safety analysis set)

	Total Efgartigimod (N=162)																			
	Cycle 1 (N=162)		Cycle 2 (N=138)		Cycle 3 (N=127)		Cycle 4 (N=107)		Cycle 5 (N=90)		Cycle 6 (N=85)		Cycle 7 (N=67)		Cycle 8 (N=57)		Cycle 9 (N=37)		Cycle 10 (N=23)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall																				
≥1 TEAE	108 (66.7)	335	69 (50.0)	154	51 (40.2)	137	47 (43.9)	92	29 (32.2)	56	27 (31.8)	45	17 (25.4)	26	13 (22.8)	20	8 (21.6)	9	4 (17.4)	5
≥1 SAE	3 (1.9)	3	8 (5.8)	9	5 (3.9)	9	5 (4.7)	5	1 (1.1)	1	4 (4.7)	8	1 (1.5)	1	2 (3.5)	2	1 (2.7)	1	0	0
≥1 TEAE of CTCAE severity grade ≥3	8 (4.9)	9	10 (7.2)	13	7 (5.5)	18	9 (8.4)	9	3 (3.3)	3	6 (7.1)	11	1 (1.5)	1	2 (3.5)	2	1 (2.7)	1	0	0
≥1 Fatal TEAE	0	0	0	0	2 (1.6)	2	2 (1.9)	2	0	0	1 (1.2)	1	0	0	0	0	0	0	0	0
≥1 Related TEAE[a]	45 (27.8)	109	16 (11.6)	28	14 (11.0)	29	13 (12.1)	23	9 (10.0)	17	10 (11.8)	13	2 (3.0)	5	4 (7.0)	5	1 (2.7)	2	1 (4.3)	2
≥1 Related SAE[a]	1 (0.6)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
≥1 TEAE leading to interruption of IMP	4 (2.5)	5	2 (1.4)	4	6 (4.7)	6	4 (3.7)	4	1 (1.1)	1	1 (1.2)	2	0	0	0	0	1 (2.7)	1	0	
≥1 TEAE leading to discontinuation of IMP	2 (1.2)	6	1 (0.7)	1	2 (1.6)	2	2 (1.9)	3	1 (1.1)	1	3 (3.5)	4	0	0	0	0	0	0	0	0
≥1 AESI[b]	49 (30.2)	59	30 (21.7)	37	23 (18.1)	28	15 (14.0)	20	5 (5.6)	5	8 (9.4)	12	6 (9.0)	6	3 (5.3)	3	3 (8.1)	3	3 (13.0)	3
≥1 IRR[c]	3 (1.9)	3	4 (2.9)	4	2 (1.6)	2	2 (1.9)	2	2 (2.2)	2	2 (2.4)	2	0	0	0	0	0	0	1 (4.3)	1

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.1.1

AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IRR=infusion-related reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per cycle; PI=principal investigator; SAE=serious adverse event; SMQ=standardized MedDRA queries; SOC=system organ class; TEAE=treatment-emergent adverse event.

[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 TEAE in the MedDRA SOC Infections and Infestations.

[c] IRRs were defined as adverse events within the SMQ (broad selection) for hypersensitivity, anaphylactic reaction, or extravasation events (excluding implants) and occurring within 48 h of an infusion, or within 2 days in case no start time was available.

Common Adverse Events

Studies ARGX-113-1704 and ARGX-113-1705

The most common TEAEs by SOC and PT reported in studies ARGX-113-1704 and ARGX-113-1705 are summarised in Table 42.

Table 42 – Common treatment-emergent adverse events, by system organ class and preferred term, in studies ARGX-113-1704 and ARGX-113-1705 (safety analysis set)

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Blood and lymphatic system disorders	2 (2.4)	3	3 (3.6)	3	5 (6.8)	5	2 (3.0)	2	7 (5.0)	7
Anaemia	1 (1.2)	1	1 (1.2)	1	3 (4.1)	3	0	0	3 (2.2)	3
Cardiac disorders	2 (2.4)	2	4 (4.8)	5	5 (6.8)	10	5 (7.6)	7	10 (7.2)	17
Atrial fibrillation	0	0	2 (2.4)	2	0	0	0	0	0	0
Cardiac failure congestive	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Palpitations	0	0	0	0	1 (1.4)	1	1 (1.5)	2	2 (1.4)	3
Tachycardia	0	0	1 (1.2)	1	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Ear and labyrinth disorders	3 (3.6)	4	1 (1.2)	2	2 (2.7)	3	1 (1.5)	1	3 (2.2)	4
Vertigo	1 (1.2)	2	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Eye disorders	7 (8.3)	11	4 (4.8)	7	0	0	1 (1.5)	5	1 (0.7)	5
Blepharospasm	2 (2.4)	3	1 (1.2)	1	0	0	0	0	0	0
Eyelid ptosis	0	0	2 (2.4)	2	0	0	1 (1.5)	1	1 (0.7)	1
Visual impairment	2 (2.4)	3	0	0	0	0	0	0	0	0
Gastrointestinal disorders	19 (22.6)	23	20 (24.1)	40	15 (20.5)	31	14 (21.2)	28	29 (20.9)	59
Abdominal pain	1 (1.2)	1	3 (3.6)	4	1 (1.4)	2	0	0	1 (0.7)	2
Abdominal pain upper	1 (1.2)	1	1 (1.2)	1	1 (1.4)	1	2 (3.0)	3	3 (2.2)	4
Diarrhoea	6 (7.1)	6	9 (10.8)	14	5 (6.8)	6	7 (10.6)	9	12 (8.6)	15
Haematochezia	0	0	0	0	1 (1.4)	1	1 (1.5)	2	2 (1.4)	3

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Nausea	7 (8.3)	7	9 (10.8)	15	5 (6.8)	8	2 (3.0)	2	7 (5.0)	10
Toothache	1 (1.2)	1	1 (1.2)	1	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Vomiting	2 (2.4)	3	2 (2.4)	2	3 (4.1)	3	3 (4.5)	6	6 (4.3)	9
General disorders and administration site conditions	8 (9.5)	14	13 (15.7)	18	9 (12.3)	13	12 (18.2)	18	21 (15.1)	31
Asthenia	1 (1.2)	1	1 (1.2)	1	1 (1.4)	1	3 (4.5)	4	4 (2.9)	5
Chest pain	1 (1.2)	1	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Chills	1 (1.2)	1	1 (1.2)	2	2 (2.7)	2	0	0	2 (1.4)	2
Cyst	0	0	0	0	0	0	2 (3.0)	2	2 (1.4)	2
Fatigue	3 (3.6)	6	2 (2.4)	2	0	0	1 (1.5)	1	1 (0.7)	1
Influenza like illness	1 (1.2)	1	2 (2.4)	3	2 (2.7)	2	0	0	2 (1.4)	2
Non-cardiac chest pain	0	0	2 (2.4)	2	0	0	0	0	0	0
Pain	2 (2.4)	2	0	0	1 (1.4)	1	1 (1.5)	2	2 (1.4)	3
Pyrexia	1 (1.2)	1	2 (2.4)	2	3 (4.1)	3	4 (6.1)	4	7 (5.0)	7
Immune system disorders	2 (2.4)	2	0	0	0	0	1 (1.5)	1	1 (0.7)	1
Seasonal allergy	2 (2.4)	2	0	0	0	0	0	0	0	0
Infections and infestations	39 (46.4)	56	31 (37.3)	42	33 (45.2)	62	32 (48.5)	54	65 (46.8)	116
Asymptomatic bacteriuria	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Bronchitis	5 (6.0)	6	2 (2.4)	2	4 (5.5)	5	0	0	4 (2.9)	5
Conjunctivitis	0	0	0	0	0	0	2 (3.0)	2	2 (1.4)	2

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
COVID-19	0	0	0	0	4 (5.5)	4	2 (3.0)	2	6 (4.3)	6
COVID-19 pneumonia	0	0	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Cystitis	0	0	2 (2.4)	3	1 (1.4)	1	2 (3.0)	3	3 (2.2)	4
Ear infection	2 (2.4)	2	0	0	0	0	0	0	0	0
Gastroenteritis	1 (1.2)	2	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Gastroenteritis viral	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Herpes zoster	0	0	0	0	4 (5.5)	4	1 (1.5)	1	5 (3.6)	5
Influenza	3 (3.6)	3	3 (3.6)	3	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Nasopharyngitis	10 (11.9)	12	15 (18.1)	17	6 (8.2)	8	9 (13.6)	11	15 (10.8)	19
Oral herpes	1 (1.2)	1	0	0	3 (4.1)	3	0	0	3 (2.2)	3
Pharyngitis	1 (1.2)	1	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Pharyngitis streptococcal	0	0	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Pneumonia	1 (1.2)	1	0	0	0	0	2 (3.0)	2	2 (1.4)	2
Respiratory tract infection	0	0	1 (1.2)	1	1 (1.4)	1	2 (3.0)	2	3 (2.2)	3
Sinusitis	2 (2.4)	2	0	0	0	0	1 (1.5)	1	1 (0.7)	1
Skin infection	0	0	0	0	0	0	2 (3.0)	4	2 (1.4)	4
Tinea versicolour	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Tracheitis	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Upper respiratory tract infection	9 (10.7)	11	4 (4.8)	5	2 (2.7)	2	3 (4.5)	4	5 (3.6)	6
Urinary tract infection	8 (9.5)	9	4 (4.8)	4	6 (8.2)	9	4 (6.1)	4	10 (7.2)	13

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Viral infection	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Viral upper respiratory tract infection	0	0	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Injury, poisoning and procedural complications	10 (11.9)	17	12 (14.5)	17	10 (13.7)	14	6 (9.1)	9	16 (11.5)	23
Contusion	3 (3.6)	3	2 (2.4)	2	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Fall	2 (2.4)	2	1 (1.2)	1	0	0	2 (3.0)	2	2 (1.4)	2
Procedural headache	4 (4.8)	4	1 (1.2)	1	3 (4.1)	4	0	0	3 (2.2)	4
Procedural pain	1 (1.2)	1	1 (1.2)	2	2 (2.7)	2	1 (1.5)	1	3 (2.2)	3
Skin abrasion	2 (2.4)	2	0	0	0	0	1 (1.5)	1	1 (0.7)	1
Investigations	2 (2.4)	3	4 (4.8)	5	5 (6.8)	6	8 (12.1)	36	13 (9.4)	42
Haemoglobin decreased	0	0	0	0	0	0	2 (3.0)	4	2 (1.4)	4
Lymphocyte count decreased	1 (1.2)	1	0	0	2 (2.7)	2	1 (1.5)	2	3 (2.2)	4
Neutrophil count increased	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Metabolism and nutrition disorders	3 (3.6)	3	5 (6.0)	5	4 (5.5)	6	2 (3.0)	2	6 (4.3)	8
Diabetes mellitus	0	0	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Hyperglycaemia	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Musculoskeletal and connective tissue disorders	17 (20.2)	20	18 (21.7)	23	15 (20.5)	20	12 (18.2)	17	27 (19.4)	37
Arthralgia	2 (2.4)	2	1 (1.2)	1	4 (5.5)	4	3 (4.5)	3	7 (5.0)	7
Back pain	4 (4.8)	4	4 (4.8)	4	4 (5.5)	4	1 (1.5)	1	5 (3.6)	5

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Muscle spasms	1 (1.2)	1	2 (2.4)	2	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Muscle twitching	0	0	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Muscular weakness	1 (1.2)	1	0	0	2 (2.7)	2	0	0	2 (1.4)	2
Myalgia	5 (6.0)	6	1 (1.2)	3	3 (4.1)	4	1 (1.5)	2	4 (2.9)	6
Neck pain	2 (2.4)	2	1 (1.2)	1	0	0	1 (1.5)	1	1 (0.7)	1
Pain in extremity	1 (1.2)	1	3 (3.6)	3	1 (1.4)	1	3 (4.5)	4	4 (2.9)	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2)	1	1 (1.2)	1	3 (4.1)	5	4 (6.1)	5	7 (5.0)	10
Squamous cell carcinoma	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Nervous system disorders	29 (34.5)	62	32 (38.6)	56	23 (31.5)	49	26 (39.4)	73	49 (35.3)	122
Dizziness	3 (3.6)	5	5 (6.0)	5	4 (5.5)	5	2 (3.0)	2	6 (4.3)	7
Headache	24 (28.6)	40	23 (27.7)	39	11 (15.1)	26	20 (30.3)	42	31 (22.3)	68
Hypoaesthesia	2 (2.4)	2	0	0	1 (1.4)	1	2 (3.0)	2	3 (2.2)	3
Migraine	2 (2.4)	3	0	0	4 (5.5)	5	1 (1.5)	1	5 (3.6)	6
Myasthenia gravis	3 (3.6)	3	3 (3.6)	3	3 (4.1)	3	1 (1.5)	1	4 (2.9)	4
Myasthenia gravis crisis	0	0	1 (1.2)	1	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Paraesthesia	2 (2.4)	2	4 (4.8)	4	0	0	1 (1.5)	1	1 (0.7)	1
Somnolence	0	0	0	0	1 (1.4)	1	1 (1.5)	13	2 (1.4)	14
Tremor	0	0	2 (2.4)	2	0	0	0	0	0	0
Renal and urinary disorders	0	0	1 (1.2)	3	2 (2.7)	2	4 (6.1)	6	6 (4.3)	8

System Organ Class Preferred Term	Study ARGX-113-1704				Study ARGX-113-1705					
	Efgartigimod (N=84)		Placebo (N=83)		Efgartigimod-Efgartigimod (N=73)		Placebo-Efgartigimod (N=66)		Total Efgartigimod (N=139)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Chronic kidney disease	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Respiratory, thoracic and mediastinal disorders	7 (8.3)	8	13 (15.7)	15	9 (12.3)	14	8 (12.1)	9	17 (12.2)	23
Cough	3 (3.6)	3	5 (6.0)	5	2 (2.7)	2	1 (1.5)	1	3 (2.2)	3
Dyspnoea	1 (1.2)	1	2 (2.4)	2	2 (2.7)	2	0	0	2 (1.4)	2
Oropharyngeal pain	3 (3.6)	3	7 (8.4)	7	1 (1.4)	1	6 (9.1)	6	7 (5.0)	7
Sinus congestion	0	0	0	0	0	0	2 (3.0)	2	2 (1.4)	2
Skin and subcutaneous tissue disorders	9 (10.7)	9	8 (9.6)	11	9 (12.3)	12	7 (10.6)	12	16 (11.5)	24
Dermatitis contact	0	0	0	0	1 (1.4)	1	1 (1.5)	1	2 (1.4)	2
Pruritus	2 (2.4)	2	1 (1.2)	1	0	0	0	0	0	0
Rash	2 (2.4)	2	2 (2.4)	2	3 (4.1)	3	2 (3.0)	5	5 (3.6)	8
Rash maculo-papular	0	0	1 (1.2)	2	1 (1.4)	1	1 (1.5)	2	2 (1.4)	3
Vascular disorders	7 (8.3)	9	6 (7.2)	6	5 (6.8)	6	4 (6.1)	5	9 (6.5)	11
Hypertension	3 (3.6)	4	6 (7.2)	6	2 (2.7)	3	3 (4.5)	4	5 (3.6)	7

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 14.3, Table 14.3.1.2.2; Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 14.3, Table 14.3.1.2
COVID-19=coronavirus disease 2019; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).
Note: The most common TEAEs were defined as those reported in ≥2 patients in either treatment group in study ARGX-113-1704 and ≥2 patients in either the efgartigimod-efgartigimod cohort or the placebo-efgartigimod cohort in study ARGX-113-1705.
Note: Efgartigimod-efgartigimod refers to the cohort of patients who received efgartigimod in the antecedent study ARGX-113-1704 and are receiving it in extension study ARGX-113-1705. Placebo-efgartigimod refers to the cohort of patients who received placebo in the antecedent study ARGX-113-1704 and are receiving efgartigimod in extension study ARGX-113-1705.
Note: A coding error was identified for the treatment-related TEAE with verbatim term "pharyngeal papilloma" in a Japanese patient. This verbatim term was erroneously coded as a PT of "oropharyngeal squamous cell carcinoma".

Pooling Block 2: All Patients with gMG who Received Efgartigimod Pool

A summary of TEAEs that occurred in ≥3 patients in the total efgartigimod group during all cycles cumulatively is presented by SOC and PT in Table 43.

In PB2, the TEAE of headache was reported in 56 (34.6%) patients in the total efgartigimod group (Table 43). In the cohort of patients who received at least 6 cycles, the frequency of the TEAE of headache in the total efgartigimod group was highest in C1 (18.8%) but lower in subsequent cycles. The TEAE of procedural headache was reported in 7 (4.3%) patients in the total efgartigimod group during all cycles cumulatively. None of the events of procedural headache were serious or resulted in interruption or discontinuation of efgartigimod. Procedural headache was CTCAE severity grade ≥3 in a single patient. Procedural headache was considered by the investigator to be related to efgartigimod in 7 (4.3%) patients in the total efgartigimod group.

Table 43 – Treatment-emergent adverse events that occurred in ≥3 patients in pooling block 2, by system organ class and preferred term (safety analysis set)

System Organ Class[a] Preferred Term	Total Efgartigimod (N=162)		
	n (%)	m	PYFU
≥1 TEAE	136 (84.0)	884	481.6
Blood and lymphatic system disorders	8 (4.9)	11	6.0
Anaemia	3 (1.9)	4	2.2
Ear and labyrinth disorders	6 (3.7)	8	4.4
Vertigo	3 (1.9)	4	2.2
Gastrointestinal disorders	46 (28.4)	88	47.9
Diarrhoea	18 (11.1)	22	12.0
Nausea	14 (8.6)	18	9.8
Vomiting	8 (4.9)	12	6.5
Abdominal pain upper	5 (3.1)	6	3.3
Abdominal pain	3 (1.9)	4	2.2
Toothache	3 (1.9)	3	1.6

System Organ Class[a] Preferred Term	Total Efgartigimod (N=162)		
	n (%)	m	PYFU
General disorders and administration site conditions	31 (19.1)	50	27.2
Pyrexia	8 (4.9)	8	4.4
Asthenia	6 (3.7)	7	3.8
Fatigue	4 (2.5)	7	3.8
Pain	4 (2.5)	5	2.7
Chest pain	3 (1.9)	3	1.6
Chills	3 (1.9)	3	1.6
Influenza like illness	3 (1.9)	3	1.6
Infections and infestations	90 (55.6)	179	97.5
Nasopharyngitis	24 (14.8)	32	17.4
Urinary tract infection	16 (9.9)	22	12.0
Upper respiratory tract infection	12 (7.4)	17	9.3
Bronchitis	8 (4.9)	11	6.0
COVID-19	6 (3.7)	6	3.3
Herpes zoster	6 (3.7)	6	3.3
Influenza	5 (3.1)	5	2.7
Oral herpes	4 (2.5)	4	2.2
Pharyngitis	4 (2.5)	4	2.2
Respiratory tract infection	4 (2.5)	4	2.2
Cystitis	3 (1.9)	4	2.2
Gastroenteritis	3 (1.9)	4	2.2
Gingivitis	3 (1.9)	3	1.6
Pneumonia	3 (1.9)	3	1.6
Sinusitis	3 (1.9)	3	1.6
Injury, poisoning and procedural complications	25 (15.4)	43	23.4
Procedural headache	7 (4.3)	8	4.4
Contusion	5 (3.1)	6	3.3
Fall	4 (2.5)	4	2.2
Procedural pain	4 (2.5)	4	2.2
Skin abrasion	3 (1.9)	3	1.6

2.6.8.3.

System Organ Class[a] Preferred Term	Total Efgartigimod (N=162)		
	n (%)	m	PYFU
Investigations	17 (10.5)	63	34.3
Lymphocyte count decreased	5 (3.1)	9	4.9
Neutrophil count increased	4 (2.5)	6	3.3
Musculoskeletal and connective tissue disorders	42 (25.9)	63	34.3
Myalgia	10 (6.2)	14	7.6
Back pain	9 (5.6)	9	4.9
Arthralgia	8 (4.9)	9	4.9
Pain in extremity	7 (4.3)	8	4.4
Muscular weakness	4 (2.5)	4	2.2
Muscle spasms	3 (1.9)	3	1.6
Neck pain	3 (1.9)	3	1.6
Nervous system disorders	72 (44.4)	198	107.9
Headache	56 (34.6)	118	64.3
Dizziness	9 (5.6)	13	7.1
Migraine	7 (4.3)	10	5.4
Myasthenia gravis	7 (4.3)	7	3.8
Hypoaesthesia	5 (3.1)	5	2.7
Paraesthesia	5 (3.1)	5	2.7
Respiratory, thoracic and mediastinal disorders	26 (16.0)	35	19.1
Oropharyngeal pain	11 (6.8)	11	6.0
Cough	7 (4.3)	7	3.8
Dyspnoea	3 (1.9)	3	1.6
Skin and subcutaneous tissue disorders	24 (14.8)	35	19.1
Rash	6 (3.7)	10	5.4
Pruritus	3 (1.9)	3	1.6
Vascular disorders	15 (9.3)	22	12.0
Hypertension	7 (4.3)	12	6.5

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.2.1.

COVID-19=coronavirus disease 2019; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per treatment; PT=preferred term; PYFU= event rate per 100 patient-years of follow-up; SOC=system organ class; TEAE=treatment-emergent adverse event

Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).

Note: Adverse events in at least 3 patients are included.

[a] Each SOC presented in the table includes the number of patients 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.

Serious adverse event/deaths/other significant events

Pooled Database 2

No treatment-emergent SAEs were reported in study ARGX-113-1602.

A summary of treatment-emergent SAEs by SOC and PT in studies ARGX-113-1704 and ARGX-113-1705 is presented in Table 44.

In PB2, in the total efgartigimod group during all cycles cumulatively, treatment-emergent SAEs that occurred in at least 3 patients were in the SOCs of Infections and Infestations and Nervous System Disorders (6 patients each [3.7%]), Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps) (5 patients [3.1%]), Cardiac Disorders and Respiratory, Thoracic and Mediastinal Disorders (3 patients each [1.9%]). Treatment-emergent SAEs in the SOC Infections and Infestations occurred in 5 (5.2%) patients in the efgartigimod group and 1 (1.5%) patient in the placebo-efgartigimod group (Table 44). In PB2, as the number of cycles increased, the frequency of treatment-emergent SAEs remained generally consistent in the total efgartigimod group.

Table 44 – Treatment-emergent serious adverse events, by system organ class and preferred term in studies ARGX-113-1704 and ARGX-113-1705 (safety analysis set)

System Organ Class Preferred Term	Study ARGX-113-1704		Study ARGX-113-1705		
	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)	Efgartigimod-Efgartigimod (N=73) n (%)	Placebo-Efgartigimod (N=66) n (%)	Total Efgartigimod (N=139) n (%)
Patient with ≥1 SAE	4 (4.8)	7 (8.4)	14 (19.2)	7 (10.6)	21 (15.1)
Blood and lymphatic system disorders	1 (1.2)	0	1 (1.4)	0	1 (0.7)
Anaemia	0	0	1 (1.4)	0	1 (0.7)
Thrombocytosis	1 (1.2)	0	0	0	0
Cardiac disorders	0	2 (2.4)	1 (1.4)	2 (3.0)	3 (2.2)
Acute myocardial infarction	0	0	0	1 (1.5)	1 (0.7)
Arrhythmia	0	0	1 (1.4)	0	1 (0.7)
Atrial fibrillation	0	1 (1.2)	0	0	0
Cardiac failure congestive	0	0	0	1 (1.5)	1 (0.7)
Defect conduction intraventricular	0	0	1 (1.4)	0	1 (0.7)
Myocardial ischaemia	0	1 (1.2)	0	0	0
Eye disorders	0	0	0	1 (1.5)	1 (0.7)
Retinal detachment	0	0	0	1 (1.5)	1 (0.7)
Gastrointestinal disorders	0	0	2 (2.7)	0	2 (1.4)
Diarrhoea	0	0	1 (1.4)	0	1 (0.7)
Irritable bowel syndrome	0	0	1 (1.4)	0	1 (0.7)
General disorders and administration site conditions	0	1 (1.2)	1 (1.4)	0	1 (0.7)
Death	0	0	1 (1.4)	0	1 (0.7)
Therapeutic product ineffective	0	1 (1.2)	0	0	0
Infections and infestations	0	1 (1.2)	5 (6.8)	1 (1.5)	6 (4.3)
COVID-19	0	0	1 (1.4)	0	1 (0.7)
COVID-19 pneumonia	0	0	2 (2.7)	0	2 (1.4)
Dysentery	0	0	1 (1.4)	0	1 (0.7)
Pneumonia	0	0	0	1 (1.5)	1 (0.7)
Pneumonia escherichia	0	0	1 (1.4)	0	1 (0.7)
Septic shock	0	0	1 (1.4)	0	1 (0.7)
Upper respiratory tract infection	0	1 (1.2)	0	0	0
Urinary tract infection	0	0	1 (1.4)	0	1 (0.7)
Injury, poisoning and procedural complications	0	2 (2.4)	1 (1.4)	0	1 (0.7)
Procedural pain	0	1 (1.2)	0	0	0
Spinal compression fracture	0	1 (1.2)	1 (1.4)	0	1 (0.7)
Musculoskeletal and connective tissue disorders	0	1 (1.2)	0	0	0
Spinal ligament ossification	0	1 (1.2)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2)	0	2 (2.7)	2 (3.0)	4 (2.9)
Adenocarcinoma of colon	0	0	0	1 (1.5)	1 (0.7)

System Organ Class Preferred Term	Study ARGX-113-1704		Study ARGX-113-1705		
	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)	Efgartigimod-Efgartigimod (N=73) n (%)	Placebo-Efgartigimod (N=66) n (%)	Total Efgartigimod (N=139) n (%)
Lung neoplasm malignant	0	0	1 (1.4)	0	1 (0.7)
Pancreatic carcinoma	0	0	0	1 (1.5)	1 (0.7)
Prostate cancer	0	0	0	1 (1.5)	1 (0.7)
Rectal adenocarcinoma	1 (1.2)	0	0	0	0
Vulval cancer	0	0	1 (1.4)	0	1 (0.7)
Nervous system disorders	1 (1.2)	3 (3.6)	3 (4.1)	2 (3.0)	5 (3.6)
Myasthenia gravis	1 (1.2)	2 (2.4)	2 (2.7)	1 (1.5)	3 (2.2)
Myasthenia gravis crisis	0	1 (1.2)	1 (1.4)	1 (1.5)	2 (1.4)
Stupor	0	0	1 (1.4)	0	1 (0.7)
Psychiatric disorders	1 (1.2)	0	0	0	0
Depression	1 (1.2)	0	0	0	0
Renal and urinary disorders	0	0	0	1 (1.5)	1 (0.7)
Bladder neck obstruction	0	0	0	1 (1.5)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	0	3 (4.1)	0	3 (2.2)
Acute respiratory failure	0	0	1 (1.4)	0	1 (0.7)
Pneumonia aspiration	0	0	1 (1.4)	0	1 (0.7)
Pulmonary embolism	0	0	1 (1.4)	0	1 (0.7)
Surgical and medical procedures	0	0	1 (1.4)	0	1 (0.7)
Spinal operation	0	0	1 (1.4)	0	1 (0.7)
Vascular disorders	0	0	1 (1.4)	0	1 (0.7)
Shock	0	0	1 (1.4)	0	1 (0.7)

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 14.3.1, Table 14.3.1.4.2; Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 14.3.1, Table 14.3.1.3
COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).
Note: Efgartigimod-efgartigimod refers to the cohort of patients who received efgartigimod in the antecedent study ARGX-113-1704 and are receiving it in extension study ARGX-113-1705. Placebo-efgartigimod refers to the cohort of patients who received placebo in the antecedent study ARGX-113-1704 and are receiving efgartigimod in extension study ARGX-113-1705.

Treatment-emergent SAEs were reported more frequently (>2 patients) in the efgartigimod-efgartigimod cohort than in the placebo-efgartigimod cohort within the SOCs of Infections and Infestations (5 patients [6.8%] vs. 1 patient [1.5%]); and Respiratory, Thoracic, and Mediastinal Disorders (3 patients [4.1%] vs. 0 patients [0.0%]).

More commonly reported treatment-emergent SAEs (>3 patients) in the total efgartigimod cohort (PB2) were in the SOCs of Infections and Infestations (6 patients [3.7%]), Nervous System Disorders (6 patients [3.7%]), and Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps) (5 patients [3.1%]).

In the pooled PB2 analysis, 11 neoplasm events were reported in 8 (4.9%) patients. Four of these 8 patients had malignancy events with aetiologies involving squamous cells, specifically squamous cell carcinoma (2 patients), oropharyngeal squamous cell carcinoma, and basosquamous carcinoma. 2 of these 4 patients had a medical history of skin cancer. Six neoplasm events reported in 5 (3.1%) patients were considered serious (PT: adenocarcinoma of the colon, lung neoplasm malignant, pancreatic carcinoma, prostate cancer, rectal adenocarcinoma, and vulval cancer). All of the events were assessed

as not related to treatment. One of the patients with a serious neoplasm event died due to stage IV lung cancer. The patient had a past history of squamous cell carcinoma and smoking, which can be considered as alternative etiology of stage IV lung cancer. One non-serious malignancy event in 1 patient was reported as probably treatment-related (oropharyngeal squamous cell carcinoma) by the Investigator. The PT term was erroneously coded as "oropharyngeal squamous cell carcinoma" and should have been coded as "pharyngeal papilloma".

With regard to treatment cycle, neoplasms were reported throughout treatment cycle 1-7, there were 4 events in treatment cycle 2, otherwise no specific pattern was seen. The onset latency of malignancy events ranged between 30 and 401 days.

With regard to studies with other FcRn antagonists, only 1 neoplasm has been reported, and it is unknown whether this report was in the placebo or active arm. In addition, no literature could be found associating chronic use of plasma exchange, immunoadsorption, and plasmapheresis therapies reducing IgGs with the development of malignancies.

Deaths

As of the 01 February 2021 data cut-off date, 5 fatal cases were reported in the efgartigimod cohorts and none in the placebo cohorts. Narratives have been provided for all 5 patients. All cases of deaths were considered not related to the study treatment by the Investigator.

From the narratives it can be observed that 2 cases of death were associated with SAE of cardiovascular disease, 1 case was related to lung cancer, 1 case was due to myasthenia crisis and 1 case was due to infections (covid-19, pneumonia, UTI and septic shock).

For the two deaths related to CV disease, both patients were elderly and known with cardiovascular disease at baseline. The patient with lung cancer had a past history of squamous cell carcinoma and smoking, which can be considered as alternative etiology of stage IV lung cancer.

Regarding the case of myasthenia crisis, the patient was AChR-Ab seropositive (please see above).

Regarding the case of death due to infections, an analysis was provided to evaluate the incidence of infectious events, relative to nadir IgG levels in pooling block 2 (PB2). It was concluded that there is no clear correlation between IgG levels and infections that are serious, of Grade ≥3, or that lead to efgartigimod treatment discontinuation. These findings are supported by literature data that indicate transient IgG reduction is not associated with an increased incidence of infection.

One patient in PB2 had an infectious event (septic shock) with a fatal outcome. The patient had a concurrent SAE of COVID-19 pneumonia that was CTCAE grade 5. The patient's nadir IgG category at the time of these events was in the third quartile. Neither event was assessed by the Investigator as related to efgartigimod. Overall, there was no clear association between reduced IgG levels and severe infections and the literature data supported this finding.

Treatment-Emergent Adverse Events of CTCAE Severity Grade ≥3

<u>Studies in Patients with Generalized Myasthenia Gravis</u>

There were no reports of TEAEs of severity Grade ≥3 in study ARGX-113-1602.

In study ARGX-113-1704, TEAEs of severity grade ≥3 occurred in 9 (10.7%) patients in the efgartigimod group and 8 (9.6%) patients in the placebo group. The only TEAE of CTCAE severity Grade ≥3 that was reported in more than 1 patient in either group was myasthenia gravis, reported in 1 (1.2%) patient in the efgartigimod group, and 2 (2.4%) patients in the placebo group.

In study ARGX-113-1705, TEAEs of severity Grade ≥3 occurred in 26 (18.7%) patients in the total efgartigimod group: in 15 (20.5%) patients in the efgartigimod-efgartigimod cohort, and in 11 (16.7%)

patients in the placebo-efgartigimod cohort. Events reported in ≥2 patients in either cohort were COVID-19 pneumonia (2 [2.7%] patients in the efgartigimod-efgartigimod cohort), headache (1 [1.4%] patient in the efgartigimod-efgartigimod cohort and 2 [3.0%] patients in the placebo-efgartigimod cohort), myasthenia gravis (2 [2.7%] patients in the efgartigimod-efgartigimod cohort and 1 [1.5%] patient in the placebo-efgartigimod cohort).

Pooled Safety Datasets

Due to the overlap of patients in the pooled safety datasets, all CTCAEs severity Grade ≥3 reported in PB1, PB2, and PB3 are described below.

TEAEs of severity Grade ≥3 occurred in 6 (6.3%) patients each in the efgartigimod and placebo groups in PB1; 32 (19.8%) patients in the total efgartigimod group during all cycles cumulatively in PB2, including 21 (21.9%) patients in the efgartigimod group and 11 (16.7%) patients in placebo-efgartigimod group; and 34 (19.0%) patients who received efgartigimod IV 10 mg/kg in PB3.

No TEAE of severity Grade ≥3 was reported in >2 patients in either treatment group in PB1. TEAEs of severity of Grade ≥3 that occurred in >2 patients in the total efgartigimod group in PB2 and in patients who received efgartigimod IV 10 mg/kg in PB3 were headache in 3 patients in PB2 (1.9%) and PB3 (1.7%) and myasthenia gravis in 4 patients in PB2 (2.5%) and PB3 (2.2%).

In PB2, there were no notable increases in the frequency of TEAEs of CTCAE severity Grade ≥3 as the number of cycles increased in the total efgartigimod group.

In general, in PB3, the profile of TEAEs of CTCAE severity Grade ≥3 in patients who received any dose of efgartigimod IV was similar to that of patients who received efgartigimod IV 10 mg/kg.

In study ARGX-113-1704, the percentage of TEAEs of severity Grade ≥3 that were reported in the patients were similar in the efgartigimod and placebo group. In study ARGX-113-1705 and PB2, the percentage of TEAEs of severity Grade ≥3 reported in the patients in the total efgartigimod group were almost double compared to the groups in study ARGX-113-1704.

Overall, there were no notable differences in the frequency of TEAEs of CTCAE severity Grade ≥3 that were reported in both PB1 and study ARGX-113-1704. The profiles of TEAEs of CTCAE severity Grade ≥3 are consistent among PB1, PB2, and PB3.

Suicidality Assessment

As recommended for studies involving an investigational product for a neurological indication, a prospective assessment for suicidal ideation and behaviour was included in studies ARGX-113-1602, ARGX-113-1704, and ARGX-113-1705. This suicidality assessment was made by asking the patient the following question from the Patient Health Questionnaire item 9 (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?"* Response options as per the PHQ-9 were limited to the following: *"not at all"*, *"several days"*, *"more than half the days"* or *"nearly every day."* This specific question was selected for the reportedly significant linear relationship between the item 9 score of the PHQ-9 and the risk of subsequent suicide attempt. Across the studies, the majority of patients had no suicidal thoughts and only 10 patients in total gave an answer different to *"not at all"*: 4 in In study ARGX-113-1704 (1 in the efgartigimod group and 3 in the placebo group) and 6 in In study ARGX-113-1705 (4 patients in the efgartigimod-efgartigimod cohort and 2 patients in the placebo-efgartigimod cohort), with no information of whether there is an overlap of the same patient(s)).

The suicidality assessment does not raise any concerns regarding efgartigimod since the answers are comparable throughout the different cohorts and only 1 patient answered *"more than half the days"* in the efgartigimod-efgartigimod cohort.

Adverse events of special interest

As efgartigimod causes a transient reduction in IgG levels, AEs in the SOC 'Infections and Infestations' has been defined as AESIs in Phase 3 clinical studies. For analysis of infections, all PTs in the MedDRA SOC 'Infections and Infestations' were retrieved.

All treatment-emergent AESIs reported in the total efgartigimod group in PB2 during all cycles cumulatively were of severity Grades 1 or 2, except for 12 events in 8 (4.9%) patients that were Grade ≥3. Treatment-emergent AESIs that were severity Grade 5 included COVID-19 pneumonia and septic shock, these reported in the same patient (n=1 [0.6%]). Treatment-emergent AESIs that were severity Grade 4 included COVID-19 pneumonia reported in 1 (0.6%) patient. Treatment-emergent AESIs that were severity Grade 3 included influenza reported in 2 (1.2%) patients and COVID-19, dysentery, pharyngitis, pharyngitis streptococcal, pneumonia, pneumonia escherichia, and UTI reported in 1 (0.6%) patient each.

An analysis was performed to evaluate the incidence of AESIs relative to nadir IgG levels. 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 is consistent with the pharmacological action of efgartigimod.

Table 45 – Treatment-emergent adverse events of special interest reported in patients in the total efgartigimod group that occurred during all cycles cumulatively in pooling block 2, by nadir IgG category, system organ class, and preferred term (safety analysis set)

	Total Efgartigimod							
	Nadir ≤P25 (N=43)		P25<Nadir≤P50 (N=39)		P50<Nadir≤P75 (N=40)		Nadir >P75 (N=40)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AESI[a]	24 (55.8)	44	25 (64.1)	52	23 (57.5)	50	18 (45.0)	33
Infections and infestations	24 (55.8)	44	25 (64.1)	52	23 (57.5)	50	18 (45.0)	33
Asymptomatic bacteriuria	1 (2.3)	1	1 (2.6)	1	0	0	0	0
Bacteriuria	0	0	1 (2.6)	1	0	0	0	0
Body tinea	0	0	1 (2.6)	1	0	0	0	0
Bronchitis	2 (4.7)	2	4 (10.3)	5	0	0	2 (5.0)	4
Candida infection	1 (2.3)	1	0	0	0	0	0	0
Conjunctivitis	0	0	2 (5.1)	2	0	0	0	0
Coronavirus infection	0	0	0	0	1 (2.5)	1	0	0
COVID-19	0	0	3 (7.7)	3	1 (2.5)	1	2 (5.0)	2
COVID-19 pneumonia	0	0	1 (2.6)	1	1 (2.5)	1	0	0
Cystitis	2 (4.7)	3	1 (2.6)	1	0	0	0	0
Dysentery	0	0	0	0	1 (2.5)	1	0	0
Ear infection	0	0	1 (2.6)	1	0	0	1 (2.5)	1
Epididymitis	0	0	1 (2.6)	1	0	0	0	0
Fungal infection	0	0	0	0	1 (2.5)	1	0	0
Gastroenteritis	0	0	1 (2.6)	1	0	0	2 (5.0)	3
Gastroenteritis viral	0	0	0	0	2 (5.0)	2	0	0

	Total Efgartigimod							
	Nadir ≤P25 (N=43)		P25<Nadir≤P50 (N=39)		P50<Nadir≤P75 (N=40)		Nadir >P75 (N=40)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Gingivitis	0	0	2 (5.1)	2	1 (2.5)	1	0	0
Helicobacter infection	0	0	0	0	1 (2.5)	1	0	0
Herpes zoster	2 (4.7)	2	1 (2.6)	1	1 (2.5)	1	2 (5.0)	2
Hordeolum	2 (4.7)	2	0	0	0	0	0	0
Influenza	1 (2.3)	1	3 (7.7)	3	0	0	1 (2.5)	1
Mastitis	0	0	0	0	0	0	1 (2.5)	1
Nail bed infection	1 (2.3)	1	0	0	0	0	0	0
Nasopharyngitis	6 (14.0)	9	5 (12.8)	5	5 (12.5)	7	8 (20.0)	11
Oral candidiasis	0	0	0	0	0	0	1 (2.5)	1
Oral herpes	1 (2.3)	1	1 (2.6)	1	2 (5.0)	2	0	0
Oropharyngeal candidiasis	0	0	1 (2.6)	1	0	0	0	0
Pharyngitis	2 (4.7)	2	1 (2.6)	1	1 (2.5)	1	0	0
Pharyngitis streptococcal	0	0	2 (5.1)	2	0	0	0	0
Pneumonia	2 (4.7)	2	0	0	0	0	1 (2.5)	1
Pneumonia escherichia	0	0	0	0	1 (2.5)	1	0	0
Pyelonephritis chronic	1 (2.3)	1	0	0	0	0	0	0
Respiratory tract infection	1 (2.3)	1	1 (2.6)	1	2 (5.0)	2	0	0
Respiratory tract infection viral	0	0	1 (2.6)	1	0	0	0	0
Rhinitis	1 (2.3)	1	0	0	0	0	0	0
Rotavirus infection	0	0	0	0	1 (2.5)	1	0	0

	Total Efgartigimod							
	Nadir ≤P25 (N=43)		P25<Nadir≤P50 (N=39)		P50<Nadir≤P75 (N=40)		Nadir >P75 (N=40)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Septic shock	0	0	0	0	1 (2.5)	1	0	0
Sialoadenitis	0	0	0	0	1 (2.5)	1	0	0
Sinusitis	0	0	1 (2.6)	1	1 (2.5)	1	1 (2.5)	1
Skin infection	1 (2.3)	2	0	0	1 (2.5)	2	0	0
Suspected COVID-19	0	0	1 (2.6)	1	0	0	0	0
Tinea versicolour	0	0	1 (2.6)	1	1 (2.5)	1	0	0
Tonsillitis	0	0	1 (2.6)	1	0	0	0	0
Tracheitis	0	0	0	0	2 (5.0)	2	0	0
Upper respiratory tract infection	5 (11.6)	7	2 (5.1)	2	5 (12.5)	8	0	0
Urinary tract infection	3 (7.0)	3	5 (12.8)	9	4 (10.0)	6	4 (10.0)	4
Viral infection	0	0	1 (2.6)	1	1 (2.5)	1	0	0
Viral pharyngitis	1 (2.3)	1	0	0	0	0	0	0
Viral tracheitis	0	0	0	0	1 (2.5)	1	0	0
Viral upper respiratory tract infection	0	0	0	0	1 (2.5)	1	1 (2.5)	1
Vulvovaginal candidiasis	0	0	0	0	1 (2.5)	1	0	0
Vulvovaginal mycotic infection	1 (2.3)	1	0	0	0	0	0	0

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.9.3

AESI=adverse event of special interest; IgG= immunoglobulin G; COVID-19=coronavirus disease 2019; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per nadir IgG category; P25=25th percentile; P50=50th percentile; P75=75th percentile; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).

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

A summary of treatment-emergent AESIs reported in the total efgartigimod group is provided by concomitant treatment for gMG, SOC, and PT in Table 46. 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.

Table 46 – Treatment-emergent adverse events of special interest reported in the total efgartigimod group that occurred during all cycles cumulatively in pooling block 2, by concomitant treatment for generalized Myasthenia Gravis, system organ class, and preferred term (safety analysis set)

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AESI[a]	15 (60.0)	24	16 (43.2)	31	9 (64.3)	19	50 (58.1)	105
Infections and infestations	15 (60.0)	24	16 (43.2)	31	9 (64.3)	19	50 (58.1)	105
Asymptomatic bacteriuria	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Bacteriuria	0	0	1 (2.7)	1	0	0	0	0
Body tinea	0	0	0	0	0	0	1 (1.2)	1
Bronchitis	1 (4.0)	1	2 (5.4)	3	0	0	5 (5.8)	7
Candida infection	0	0	0	0	0	0	1 (1.2)	1
Conjunctivitis	0	0	0	0	0	0	2 (2.3)	2
Coronavirus infection	0	0	0	0	0	0	1 (1.2)	1
COVID-19	2 (8.0)	2	0	0	1 (7.1)	1	3 (3.5)	3
COVID-19 pneumonia	0	0	0	0	0	0	2 (2.3)	2
Cystitis	0	0	1 (2.7)	2	0	0	2 (2.3)	2
Dysentery	0	0	0	0	0	0	1 (1.2)	1
Ear infection	0	0	0	0	1 (7.1)	1	1 (1.2)	1
Epididymitis	0	0	1 (2.7)	1	0	0	0	0
Fungal infection	0	0	1 (2.7)	1	0	0	0	0
Gastroenteritis	0	0	0	0	1 (7.1)	2	2 (2.3)	2
Gastroenteritis viral	1 (4.0)	1	1 (2.7)	1	0	0	0	0

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Gingivitis	0	0	0	0	1 (7.1)	1	2 (2.3)	2
Helicobacter infection	0	0	1 (2.7)	1	0	0	0	0
Herpes zoster	0	0	0	0	1 (7.1)	1	5 (5.8)	5
Hordeolum	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Influenza	1 (4.0)	1	1 (2.7)	1	0	0	3 (3.5)	3
Mastitis	0	0	0	0	1 (7.1)	1	0	0
Nail bed infection	0	0	0	0	0	0	1 (1.2)	1
Nasopharyngitis	6 (24.0)	7	3 (8.1)	4	2 (14.3)	4	13 (15.1)	17
Oral candidiasis	0	0	0	0	0	0	1 (1.2)	1
Oral herpes	0	0	0	0	1 (7.1)	1	3 (3.5)	3
Oropharyngeal candidiasis	0	0	1 (2.7)	1	0	0	0	0
Pharyngitis	2 (8.0)	2	1 (2.7)	1	0	0	1 (1.2)	1
Pharyngitis streptococcal	0	0	0	0	0	0	2 (2.3)	2
Pneumonia	0	0	1 (2.7)	1	0	0	2 (2.3)	2
Pneumonia escherichia	1 (4.0)	1	0	0	0	0	0	0
Pyelonephritis chronic	0	0	0	0	0	0	1 (1.2)	1
Respiratory tract infection	0	0	0	0	0	0	4 (4.7)	4
Respiratory tract infection viral	0	0	0	0	0	0	1 (1.2)	1
Rhinitis	0	0	0	0	0	0	1 (1.2)	1
Rotavirus infection	0	0	0	0	0	0	1 (1.2)	1

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Septic shock	0	0	0	0	0	0	1 (1.2)	1
Sialoadenitis	0	0	0	0	0	0	1 (1.2)	1
Sinusitis	0	0	0	0	2 (14.3)	2	1 (1.2)	1
Skin infection	0	0	1 (2.7)	2	0	0	1 (1.2)	2
Suspected COVID-19	1 (4.0)	1	0	0	0	0	0	0
Tinea versicolour	0	0	0	0	0	0	2 (2.3)	2
Tonsillitis	0	0	0	0	0	0	1 (1.2)	1
Tracheitis	0	0	0	0	0	0	2 (2.3)	2
Upper respiratory tract infection	3 (12.0)	4	2 (5.4)	2	1 (7.1)	2	6 (7.0)	9
Urinary tract infection	3 (12.0)	4	3 (8.1)	5	1 (7.1)	3	9 (10.5)	10
Viral infection	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Viral pharyngitis	0	0	1 (2.7)	1	0	0	0	0
Viral tracheitis	0	0	0	0	0	0	1 (1.2)	1
Viral upper respiratory tract infection	0	0	0	0	0	0	2 (2.3)	2
Vulvovaginal candidiasis	0	0	0	0	0	0	1 (1.2)	1
Vulvovaginal mycotic infection	0	0	0	0	0	0	1 (1.2)	1

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.9.2

AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per standard of care category; PT=preferred term; SOC=system organ class; AESI=adverse event of special interest; NSID=nonsteroidal immunosuppressive drug; ST=steroids

Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).

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

In study ARGX-113-1704, 46.4% of the patients in the efgartigimod group and 37.3% of the patients in the placebo group reported treatment-emergent AESIs. The most frequently reported treatment-emergent AESIs in the overall population were: nasopharyngitis, upper respiratory tract infection, urine tract infections and bronchitis. Except for nasopharyngitis, all AESIs in the overall population were reported more frequently in the efgartigimod group compared to the placebo group.

In the total efgartigimod group in study ARGX-113-1705, AESIs were reported in 46.8% of the patients. The most frequent AESIs reported in the total efgartigimod group were: nasopharyngitis, urinary tract infection, COVID-19, herpes zoster and upper respiratory tract infection.

Eight serious AESIs were reported in 6 patients (4.3%): COVID-19, COVID-19 pneumonia (2 patients), dysentery, pneumonia, pneumonia escherichia, septic shock and urinary tract infection. Candidiasis and herpetic infections were reported in 11 (7.9%) patients in the total efgartigimod group: herpes zoster (3.6%), oral herpes (2.2%), oral candidiasis (0.7%), oropharyngeal candidiasis (0.7%) and vulvovaginal candidiasis (0.7%).

In PB2, treatment-emergent AESIs occurred in 90 (55.6%) patients in the total efgartigimod group. The most frequently reported treatment-emergent AESIs by PT were similar to study ARGX-113-1704 and ARGX-113-1705. 8 (4.9%) patients had reported AESIs that were of severity grade ≥3.

Serious treatment-emergent AESIs occurred in 3.7% of the patients in the total efgartigimod group during all cycles cumulatively. Treatment-emergent AESIs that were considered by the Investigator to be related to efgartigimod were reported in 13 (8.0%) patients in the total efgartigimod group during all cycles cumulatively, and the only PT reported in more than 2 patients was herpes zoster (4 [2.5%] patients. In the total efgartigimod group during all cycles cumulatively, herpes zoster occurred in 6 (3.7%) patients, oral herpes occurred in 4 (2.5%) patients, and oral candidiasis, oropharyngeal candidiasis, candida infection, vulvovaginal candidiasis and vulvovaginal mycotic infection occurred in 1 (0.6%) patient each. As observed above and as expected, efgartigimod treatment seems to be associated with an increase in the frequency of infections.

2.6.8.4. Laboratory findings

Studies ARGX-113-1704 and ARGX-113-1705

A summary of worst-case CTCAE severity Grade ≥3 abnormalities in clinical chemistry and haematology in any cycle in studies ARGX-113-1704 and ARGX-113-1705 is presented in Table 47.

In study ARGX-113-1704, lymphocyte count decreased was the most frequently reported Grade ≥3 abnormality, occurring in 8 (9.5%) patients in the efgartigimod group and 8 (9.6%) patients in the placebo group.

In study ARGX-113-1705, there were no clinically meaningful mean changes from baseline in the clinical chemistry or haematology parameters or any noteworthy differences in mean changes between the cohorts of patients who received efgartigimod or placebo in the previous study. There was a low incidence of abnormal values in clinical chemistry and haematology parameters with no clinically relevant changes observed in the laboratory parameters analysed.

The majority of clinical chemistry and haematology abnormalities at any time post-baseline (over all of the cycles of treatment) were of severity CTCAE Grade ≤2 with similar numbers of patients reporting laboratory abnormalities in the cohorts of patients who received efgartigimod or placebo in the previous study. The most frequently reported Grade ≥3 abnormalities were lymphocyte count decreased (13 [9.4%]) followed by hypertriglyceridemia (4 [3.0%]), and high cholesterol (2 [1.5%]). All worst-case

laboratory abnormalities were Grade 3 except for a single instance of Grade 4 lymphocyte count decreased in 1 (0.7%) patient.

Table 47 – Laboratory abnormalities of CTCAE grade ≥3 severity in all cycles in studies ARGX-113-1704 and ARGX-113-1705 (safety analysis set)

	Study ARGX-113-1704		Study ARGX-113-1705		
	Efgartigimod (N=84) n / N (%)	Placebo (N=83) n / N (%)	Efgartigimod-Efgartigimod (N=73) n / N (%)	Placebo-Efgartigimod (N=66) n / N (%)	Total Efgartigimod (N=139) n / N (%)
Chemistry					
Alanine aminotransferase increased	0 / 84	1 / 83 (1.2)	0 / 72	0 / 66	0 /138
Grade 3	0 / 84	1 / 83 (1.2)	0 / 72	0 / 66	0 /138
Cholesterol high	0 / 83	3 / 82 (3.7)	0 / 67	2 / 65 (3.1)	2 /132 (1.5)
Grade 3	0 / 83	3 / 82 (3.7)	0 / 67	2 / 65 (3.1)	2 /132 (1.5)
GGT increased	0 / 84	1 / 83 (1.2)	0 / 72	0 / 66	0 /138
Grade 3	0 / 84	1 / 83 (1.2)	0 / 72	0 / 66	0 /138
Hypernatremia	2 / 84 (2.4)	0 / 83	0 / 72	0 / 66	0 /138
Grade 3	1 / 84 (1.2)	0 / 83	0 / 72	0 / 66	0 /138
Grade 4	1 / 84 (1.2)	0 / 83	0 / 72	0 / 66	0 /138
Hypertriglyceridemia	2 / 83 (2.4)	1 / 82 (1.2)	0 / 67	4 / 65 (6.2)	4 /132 (3.0)
Grade 3	2 / 83 (2.4)	1 / 82 (1.2)	0 / 67	4 / 65 (6.2)	4 /132 (3.0)
Hematology					
Activated partial thromboplastin time prolonged	0 / 84	0 / 83	0 / 72	1 / 66 (1.5)	1 /138 (0.7)
Grade 3	0 / 84	0 / 83	0 / 72	1 / 66 (1.5)	1 /138 (0.7)
Lymphocyte count decreased	8 / 84 (9.5)	8 / 83 (9.6)	6 / 72 (8.3)	7 / 66 (10.6)	13 /138 (9.4)
Grade 3	8 / 84 (9.5)	8 / 83 (9.6)	6 / 72 (8.3)	6 / 66 (9.1)	12 /138 (8.7)
Grade 4	0 / 84	0 / 83	0 / 72	1 / 66 (1.5)	1 /138 (0.7)
Neutrophil count decreased	0 / 84	1 / 83 (1.2)	0 / 72	2 / 66 (3.0)	2 /138 (1.4)
Grade 3	0 / 84	1 / 83 (1.2)	0 / 72	2 / 66 (3.0)	2 /138 (1.4)
White blood cell decreased	0 / 84	1 / 83 (1.2)	0 / 72	1 / 66 (1.5)	1 /138 (0.7)
Grade 3	0 / 84	1 / 83 (1.2)	0 / 72	1 / 66 (1.5)	1 /138 (0.7)

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 12.4.2.3, Table 48; Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 12.4.2.3, Table 35; and Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 14.3.2.3

CTCAE=Common Terminology Criteria for Adverse Events; GGT=gamma-glutamyl transferase; n=number of patients for whom the observation was reported; N=number of patients in the analysis set with data.

Note: Worst-case analysis considering all postbaseline assessments (over all cycles), including unscheduled assessments.

Note: Efgartigimod-efgartigimod refers to the cohort of patients who received efgartigimod in the antecedent study ARGX-113-1704 and are receiving it in extension study ARGX-113-1705. Placebo-efgartigimod refers to the cohort of patients who received placebo in the antecedent study ARGX-113-1704 and are receiving efgartigimod in extension study ARGX-113-1705.

Pooling Block 2: All Patients with gMG who Received Efgartigimod Pool

There were no clinically meaningful mean changes from baseline in the clinical chemistry or haematology parameters. The majority of clinical chemistry and haematology abnormalities at any time post-baseline (during all cycles of treatment) were of CTCAE grade ≤2 severity.

A summary of worst-case Grade ≥3 abnormalities in clinical chemistry and haematology is presented in Table 48. The only Grade ≥3 laboratory abnormality reported in ≥10% of patients was Grade 3 lymphocyte count decreased. The only Grade 4 laboratory abnormalities were lymphocyte count decreased and hypernatremia. The only Grade ≥3 chemistry laboratory abnormality reported in ≥3% of patients was Grade 3 hypertriglyceridemia. There was no reduction in levels of serum albumin, and no events of hypoalbuminemia were reported with the administration of efgartigimod.

Table 48 – Worst laboratory abnormalities of CTCAE grade ≥3 severity reported in patients in the total efgartigimod group in pooling block 2 (safety analysis set)

	Total Efgartigimod (N=162) n / N (%)
Chemistry	
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)

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.2.2.3.2
CTCAE=Common Terminology for Adverse Events; n=number of patients for whom the observation was reported; N=number of patients in the analysis set with data.
Note: Worst-case analysis considering all postbaseline assessments (all cycles), including unscheduled assessments.

The majority of clinical chemistry and haematology abnormalities at any time post-baseline were of severity CTCAE Grade ≤2 with similar numbers of patients reporting laboratory abnormalities in the cohorts of patients who received efgartigimod or placebo in the previous study. No patients fulfilled the criteria for Hy's law i.e., no patients experienced alanine aminotransferase or aspartate aminotransferase increases ≥3 times upper limit of normal and a total bilirubin ≥2 times upper limit of normal.

High cholesterol was seen both in the placebo cohort in study ARG-113-1704 in 3 patients (3.7%) and in the placebo-efgartigimod cohort in study ARG-113-1705 in 2 patients (3.1%). Hypertriglyceridemia was seen in the efgartigimod cohort both in study ARG-113-1704 in 2 patients (2.4%) and in the placebo-efgartigimod cohort in study ARG-113-1705 in 4 patients (6.2%) and in the placebo cohort in 1 patient (1.2%) in study ARG-113-1704. The Applicant presented an evaluation of the laboratory abnormalities of high cholesterol and hypertriglyceridemia in the studies ARGX-113-1704 and ARGX-113-1705. In study ARGX-113-1704, a worst-case shift from baseline in the laboratory abnormality of CTCAE Grade 3 cholesterol high was not reported in patients in the efgartigimod group. A worst-case shift from baseline in the laboratory abnormality of CTCAE Grade 3 hypertriglyceridemia was reported in 2 patients in the efgartigimod group and 1 patient in the placebo group during study ARGX-113-1704. The Applicant

states that no TEAEs under the SOCs 'Cardiac disorders' or 'vascular disorders' were reported in the patients in the efgartigimod group who had Grade 3 hypertriglyceridemia during study ARGX-113-1704. A worst-case shift from baseline in the laboratory abnormality of CTCAE Grade 3 hypertriglyceridemia was not reported in patients in the efgartigimod-efgartigimod cohort and in 4 patients in the placebo-efgartigimod cohort during study ARGX-113-1705. A worst-case shift from baseline in the laboratory abnormality of CTCAE Grade 3 cholesterol high was reported in no patients in the efgartigimod-efgartigimod cohort and 2 patients in the placebo-efgartigimod cohort during study ARGX-113-1705. In study ARGX-113-1705, 2 patients who had Grade 3 cholesterol high or hypertriglyceridemia also had TEAEs under the SOCs 'Cardiac disorders' and 'Vascular disorders'. None of the events were assessed by the investigator as related to efgartigimod treatment. In conclusion, no association with laboratory abnormalities of hypertriglyceridemia or high cholesterol and efgartigimod was found.

Hypernatremia was only seen on the efgartigimod cohort in study ARG-113-1704 in 2 patients (2.4%).

Lymphocyte count decreased in 8 (9.5%) patients in the efgartigimod group and 8 (9.6%) patients in the placebo group in study ARG-113-1704 and 13 (9.4%) patients in the total efgartigimod cohort in study ARG-113-1705.

Vital signs

General Vital Signs: Studies ARGX-113-1704 and ARGX-113-1705 and PB2

There were no notable changes from baseline in vital sign parameters (heart rate, systolic BP, and diastolic BP), neither by cycle in the overall population nor over time in the overall population. The Applicant states that overall, no trends in vital sign measurements or physical examination abnormalities were observed throughout all studies and in the polling blocks.

In study ARGX-113-1704, there were no notable changes from baseline in vital sign parameters (heart rate, systolic and diastolic BP) or differences between the efgartigimod and placebo groups. There were no imbalances in the number of patients with clinically relevant physical examination findings between the efgartigimod and placebo groups.

In study ARGX-113-1705, there were no notable changes from baseline in vital sign parameters (heart rate, systolic BP, diastolic BP, or temperature) or differences between the efgartigimod-efgartigimod and placebo-efgartigimod cohorts.

Overall, in both studies, outliers from normal ranges were comparable in the different cohorts.

Electrocardiogram, Studies ARGX-113-1704 and ARGX-113-1705

A summary of patients with worst-case severe abnormalities in ECG evaluations in studies ARGX-113-1704 and ARGX-113-1705 is presented in Table 49, the most pronounced difference was an imbalance of patients treated with efgartigimod experiencing an QTcF interval increase of 30-60msec; 23.5% in the total efgartigimod group (Trial ARGX-113-1705) vs. 16.9% in the placebo group (Trial ARGX-113-1704). Please see PB2 below.

Table 49 – Most severe abnormalities in electrocardiogram parameters in any cycle in studies ARGX-113-1704 and ARGX-113-1705 (safety analysis set)

	Study ARGX-113-1704		Study ARGX-113-1705		
	Efgartigimod (N=84) n / N (%)	Placebo (N=83) n / N (%)	Efgartigimod-Efgartigimod (N=73) n / N (%)	Placebo-Efgartigimod (N=66) n / N (%)	Total Efgartigimod (N=139) n / N (%)
Heart Rate (bpm)					
High (>100)	3 / 84 (3.6)	6 / 83 (7.2)	3 / 72 (4.2)	2 / 66 (3.0)	5 /138 (3.6)
PR Interval (ms)					
Low (<120)	6 / 83 (7.2)	12 / 83 (14.5)	4 / 72 (5.6)	9 / 66 (13.6)	13 /138 (9.4)
High (>220)	3 / 83 (3.6)	3 / 83 (3.6)	2 / 72 (2.8)	2 / 66 (3.0)	4 /138 (2.9)
QRS Interval (ms)					
High (>120)	6 / 84 (7.1)	6 / 83 (7.2)	3 / 72 (4.2)	4 / 66 (6.1)	7 /138 (5.1)
QTcF Interval (ms)					
]450; 480]	6 / 84 (7.1)	8 / 83 (9.6)	4 / 72 (5.6)	10 / 66 (15.2)	14 /138 (10.1)
]480; 500]	1 / 84 (1.2)	0 / 83	1 / 72 (1.4)	1 / 66 (1.5)	2 /138 (1.4)
Change from baseline of]30; 60]	13 / 84 (15.5)	14 / 83 (16.9)	11 / 70 (15.7)	21 / 66 (31.8)	32 /136 (23.5)
Change from baseline of >60	0 / 84	1 / 83 (1.2)	1 / 70 (1.4)	0 / 66	1 /136 (0.7)

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Section 12.5.3, Table 49; Module 5.3.5.2, ARGX-113-1705 CSR IA 3, Section 12.5.2, Table 36; Module 5.3.2.5, ARGX-113-1705 CSR IA 3, Section 14.3, Tables 14.3.4.2 and 14.3.4.3.
bpm=beats per minute; ms=milliseconds; n=number of patients for whom the observation was reported; N=number of patients in the analysis set with data.
Note: Most severe abnormalities considering all postbaseline assessments (over all of the cycles), including unscheduled assessments.
Note: Efgartigimod-efgartigimod refers to the cohort of patients who received efgartigimod in the antecedent study ARGX-113-1704 and are receiving it in extension study ARGX-113-1705. Placebo-efgartigimod refers to the cohort of patients who received placebo in the antecedent study ARGX-113-1704 and are receiving efgartigimod in extension study ARGX-113-1705.

Electrocardiogram, Pooling Block 2: All Patients with gMG who Received Efgartigimod Pool

A summary of patients with the most severe ECG abnormalities is presented in Table 50. Considering the longer duration of the observation period in PB2, there were no substantial differences in ECG abnormalities between PB2 and the efgartigimod group in PB1. With the longer follow-up duration, an increase in the overall incidence of randomly occurring events irrespective of causality is expected. Accordingly, a higher percentage of patients in PB2 had a QTcF increase from baseline of >30 to ≤60 ms compared to PB1 (22.8% and 9.4%, respectively) with mean (SD) follow-up durations of 413.9 (170.26) days and 91.9 (36.99) days, respectively. A QTcF increase from baseline >60 ms was observed in 2 (1.2%) patients (one patient is also included in PB1).

Table 50 – Most severe abnormalities in electrocardiogram parameters reported in the total efgartigimod group in pooling block 2 (safety analysis set)

	Total Efgartigimod (N=162) n / N (%)
HR (bpm)	
High	6 /162 (3.7)
PR (ms)	
Low	18 /161 (11.2)
High	5 /161 (3.1)
QRS (ms)	
High	11 /162 (6.8)
QTcF (ms)	
]450; 480]	20 /162 (12.3)
]480; 500]	3 /162 (1.9)
]30; 60]	37 /162 (22.8)
>60	2 /162 (1.2)

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.4.2.2.2 and 14.3.4.2.3.2

HR=heart rate; bpm=beats per minute; ms=milliseconds; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per treatment; 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.

A post-infusion QTcF interval measurement between >480 to ≤500 ms was reported in 3 (1.9%) patients in the PB2 and none in the placebo cohorts. Two (1.2%) had a QTcF interval increase from baseline of >60 ms in PB2 and 1 (1.2%) in the placebo cohort in study ARGX-113-1704.

In study ARGX-113-1705, 21 (31.8%) in the placebo-efgartigimod group had a QTcF interval increase from baseline of [30,60] ms, compared to 11 (15.7%) in the efgartigimod-efgartigimod cohort. Post-infusion QTcF interval measurement between >450 to ≤480 ms were reported in 10 (15.2%) patients in the placebo-efgartigimod cohort compared to 4 (5.6%) patients in the efgartigimod-efgartigimod cohort. Upon request and based on further analyses, the Applicant argues that the higher third quartile (Q3; 75th percentile) value in the placebo-efgartigimod cohort provides a potential explanation for the difference in the rates of worst abnormalities in the >450 to ≤480 ms range as further analyses of the data has shown that 25% of the highest baseline QTcF values in the placebo-efgartigimod cohort were >421 ms, which was noticeable higher than observed in the efgartigimod-efgartigimod group (with the 25% of the highest baseline QTcF values being >414.0 ms). This may be the actual explanation.

In the Phase 1 study ARGX-113-1501 Part 1 (SAD) and 2 (MAD), none of the ECG abnormalities reported were considered by the Investigator to be clinically significant, and no ECG-related TEAEs were reported. In the q4d regimen in Part 2 (MAD), a QTcF interval increase from baseline of [30,60] ms was reported in subjects receiving efgartigimod IV 10 mg/kg; however, no cardiac-related TEAEs were reported in these subjects.

In the Phase 1 study ARGX-113-1702, there were isolated ECG abnormalities in all treatment groups, and none were considered by the investigator to be clinically significant. Overall, no values of ECG parameters exhibit any pattern which can signify any relationship with the dose (amount) of IMP or time following the administration of the IMP in any treatment group. There were no clinically meaningful differences in ECG parameters between Treatments A and D.

2.6.8.5. In vitro biomarker test for patient selection for safety

There are no *in vitro* biomarker tests relevant for patient selection for safety.

2.6.8.6. Safety in special populations

An overview of AEs by age groups is provided for PB2 in the table below.

Table 51 – Adverse events – all patients with MG who received efgartigimod: adverse events overview by age category

ANALYSIS SET: SAFETY

ALL PATIENTS (AChR-Ab SEROPOSITIVE + AChR-Ab SERONEGATIVE)
ANY CYCLE

	TOTAL EFGARTIGIMOD (N=162)					
	18 - <65 years (N=137)			>=65 years (N=25)		
TOTAL NUMBER OF PATIENTS WITH:	n	(%)	m	n	(%)	m
AT LEAST ONE TEAE	116	(84.7)	753	20	(80.0)	131
AT LEAST ONE SERIOUS TEAE	18	(13.1)	26	7	(28.0)	13
AT LEAST ONE GRADE >= 3 TEAE	25	(18.2)	42	7	(28.0)	25
AT LEAST ONE FATAL TEAE	2	(1.5)	2	3	(12.0)	3
AT LEAST ONE TREATMENT-RELATED TEAE ACCORDING TO PI	54	(39.4)	208	9	(36.0)	25
AT LEAST ONE SERIOUS TREATMENT-RELATED TEAE	1	(0.7)	1	0		
AT LEAST ONE TEAE LEADING TO INTERRUPTION OF STUDY DRUG	15	(10.9)	21	1	(4.0)	2
AT LEAST ONE TEAE LEADING TO DISCONTINUATION OF STUDY DRUG	10	(7.3)	16	1	(4.0)	1
AT LEAST ONE TEAE OF SPECIAL INTEREST	79	(57.7)	156	11	(44.0)	23
AT LEAST ONE INFUSION-RELATED REACTION	12	(8.8)	15	1	(4.0)	1

n = NUMBER OF PATIENTS WITH EVENT (PATIENTS 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 PATIENTS IN THE SAFETY ANALYSIS SET PER TREATMENT, CYCLE AND SUBGROUP.
TREATMENT-RELATED IS DEFINED AS AT LEAST POSSIBLY DRUG RELATED ACCORDING TO THE INVESTIGATOR, OR A MISSING DRUG RELATEDNESS.

A review of the overview of TEAEs and TEAEs by MedDRA SOC and PT overall and by cycle in PB2 identified a similar tolerability profile between patients <65 years and ≥65 years. Specifically, this observation was consistent for the SOC 'Infections and Infestations'. Three deaths occurred in patients ≥65 years; however, for all 3 patients, the cause of death was not considered by the Investigator to be related to efgartigimod.

The percentage of Serious TEAEs and ≥1 TEAE of CTCAE severity Grade ≥3 were higher in the patient group ≥65 years (28,0% and 28,0%) than the patient group <65 years (13,1% and 18,2%). It is noted that none of the (S)TEAEs Grade ≥3 were reported in more than 1 patient ≥65 years of age. It is expected that an elderly population may overall have a higher frequency of co-morbidities, which will increase the risk of AEs not necessarily related to study treatment.

<u>Sex</u>

An overview of AEs by sex is provided for PB2 in Table 52.

Table 52 - Adverse events – all patients with MG who received efgartigimod: adverse events overview by gender

ANALYSIS SET: SAFETY

ALL PATIENTS (AChR-Ab SEROPOSITIVE + AChR-Ab SERONEGATIVE)
ANY CYCLE

TOTAL NUMBER OF PATIENTS WITH:	TOTAL EFGARTIGIMOD (N=162) MALE (N=45) n	(%)	m	FEMALE (N=117) n	(%)	m
AT LEAST ONE TEAE	36	(80.0)	222	100	(85.5)	662
AT LEAST ONE SERIOUS TEAE	11	(24.4)	21	14	(12.0)	18
AT LEAST ONE GRADE >= 3 TEAE	13	(28.9)	35	19	(16.2)	32
AT LEAST ONE FATAL TEAE	3	(6.7)	3	2	(1.7)	2
AT LEAST ONE TREATMENT-RELATED TEAE ACCORDING TO PI	19	(42.2)	57	44	(37.6)	176
AT LEAST ONE SERIOUS TREATMENT-RELATED TEAE	0			1	(0.9)	1
AT LEAST ONE TEAE LEADING TO INTERRUPTION OF STUDY DRUG	4	(8.9)	5	12	(10.3)	18
AT LEAST ONE TEAE LEADING TO DISCONTINUATION OF STUDY DRUG	4	(8.9)	4	7	(6.0)	13
AT LEAST ONE TEAE OF SPECIAL INTEREST	23	(51.1)	47	67	(57.3)	132
AT LEAST ONE INFUSION-RELATED REACTION	2	(4.4)	3	11	(9.4)	13

n = NUMBER OF PATIENTS WITH EVENT (PATIENTS 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 PATIENTS IN THE SAFETY ANALYSIS SET PER TREATMENT, CYCLE AND SUBGROUP.
TREATMENT-RELATED IS DEFINED AS AT LEAST POSSIBLY DRUG RELATED ACCORDING TO THE INVESTIGATOR, OR A MISSING DRUG RELATEDNESS.

In PB2 headache was reported at a higher frequency in females (43 [36,8%] patients) than males (13 [28,9%] patients) in the total efgartigimod group. This is consistent with differences reported by gender for tension-type headache and chronic daily headache in the general population.

Race and Bodyweight

Due to low patients in the subgroups, limited conclusions can be drawn. However, no clinically meaningful differences were identified.

Seropositive and Seronegative

In PB2, selected safety data were provided by AChR-Ab seropositive or seronegative status. Safety results from this subgroup analysis were consistent between AChR-Ab seropositive patients and AChR-Ab seronegative patients. Overall, TEAEs were reported in 102 (81.6%) AChR-Ab seropositive patients, and 34 (91.9%) AChR-Ab seronegative patients. No trends or patterns were observed between the 2 patient populations that indicate a clinically meaningful difference in the safety profiles.

The available data shows that acetylcholine receptor (AChR) antibodies (Ab) are detected in the serum of more than 80-90% patients with generalised myasthenia gravis. In the present data-set (total n=162), 77% (n=125) were AChR-Ab positive. Overall, among the AChR-Ab positive patients there were more patients with ≥1 SAE, more patients with ≥1 TEAE of CTCAE severity Grade ≥3 and more patients with ≥1 related fatal and related TEAE. On the contrary, among patients who were AChR-Ab negative there was a higher frequency of patients with ≥1 TEAE, patients with ≥1 TEAE leading to interruption and discontinuation of study medication and patients with ≥1 AESI and ≥1 IRR. All but one patients (5/6 ≈83%) who developed myasthenia crisis were AChR-Ab positive. Nevertheless, as the indication is restricted to only 'adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive' the differences in AChR-Ab status is not considered important, and overall, the safety profile as observed in AChR-Ab positive patients does not compromise the benefit-risk assessment.

Hepatic Impairment

No dedicated pharmacokinetic study has been performed in patients with hepatic impairment, and no patients with hepatic impairment was included in the clinical studies. Therefore, 'Hepatic impairment' has been included as Missing information in the RMP. In the popPK analysis, hepatic function markers

did not affect the PK of efgartigimod. Due to the nature of the product, an impact of hepatic impairment is not expected. Sufficient information regarding patients with hepatic impairment is included in the SmPC (sections 4.2 and 5.2.)

The impact of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of efgartigimod has not been studied; however, an effect requiring a dose adjustment for patients with hepatic impairment is unlikely to be present. Markers of hepatic function were also evaluated as potential covariates in the population PK/PD analysis. Albumin, total bilirubin, aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase did not influence any of the model parameters in the final population PK/PD model.)

Renal impairment

With a molecular weight of approximately 54 kDa, efgartigimod is at the boundary of molecules that are renally filtered. After a single dose of efgartigimod IV 10 mg/kg in healthy subjects, less than 0.1% of the administered dose was recovered in urine.

During all cycles in study ARGX-113-1704, shifts in eGFR category from study entry baseline category to the worst post-baseline category were similar between the efgartigimod and placebo groups in patients with normal renal function and mild renal impairment at baseline (Table 53):

Table 53 – Laboratory data: cross tabulation of worst eGFR categories versus baseline (all patients)

ANALYSIS SET: SAFETY

PARAMETER = ESTIMATED GLOMERULAR FILTRATION RATE (mL/min/1.73m2)

								SEB eGFR CATEGORY					
	WORST eGFR CATEGORY	T	%	T'	%	cT'	%	NORMAL		MILD IMPAIRED		MODERATE IMPAIRED	
OVERALL													
EFGARTIGIMOD	SEVERE IMPAIRED												
	MODERATE IMPAIRED	7	8.3	5	6.0	5	6.0			5	6.0	2	2.4
	MILD IMPAIRED	43	51.2	25	29.8	30	35.7	25	29.8	18	21.4		
	NORMAL	34	40.5					33	39.3			1	1.2
	TOTAL	84	100	30	35.7			58	69.0	23	27.4	3	3.6
PLACEBO	SEVERE IMPAIRED	1	1.2	1	1.2	1	1.2					1	1.2
	MODERATE IMPAIRED	6	7.2	3	3.6	4	4.8			3	3.6	3	3.6
	MILD IMPAIRED	44	53.0	17	20.5	21	25.3	17	20.5	27	32.5		
	NORMAL	32	38.6					31	37.3	1	1.2		
	TOTAL	83	100	21	25.3			48	57.8	31	37.3	4	4.8

T = TOTAL PER eGFR CATEGORY WITHIN EACH TREATMENT AND CYCLE.
T' = TOTAL WITH A TREATMENT-EMERGENT ABNORMAL eGFR CATEGORY WITHIN EACH TREATMENT AND CYCLE.
cT'= CUMULATIVE TOTAL OVER DECREASING ABNORMAL eGFR CATEGORIES OF PATIENTS WITH A TREATMENT-EMERGENT ABNORMAL eGFR CATEGORY WITHIN EACH TREATMENT AND CYCLE.
SEB = STUDY ENTRY BASELINE, LAST AVAILABLE VALUE PRIOR TO FIRST ADMINISTRATION OF THE IMP IN THE FIRST CYCLE.
eGFR CATEGORY: NORMAL >= 90 mL/min/1.73m2 > MILD IMPAIRED >= 60 mL/min/1.73m2 > MODERATE IMPAIRED >= 30 mL/min/1.73m2 > SEVERE IMPAIRED.
THE WORST eGFR CATEGORY CONSIDERS ALL POST-BASELINE ASSESSMENTS WITHIN THE PERIOD, INCLUDING UNSCHEDULED ASSESSMENTS.
THE DENOMINATOR FOR THE PERCENTAGE CALCULATIONS IS THE TOTAL NUMBER OF PATIENTS PER TREATMENT AND PER CYCLE IN THE SAFETY ANALYSIS SET, EXCLUDING MISSING VALUE.

In study ARGX-113-1704, Shifts in eGFR category from study entry baseline category to the worst post-baseline category were similar between the efgartigimod and placebo groups in patients with normal renal function and mild renal impairment at baseline; 25 (29.8%) and 17 (20.5%) patients, respectively, shifted from normal renal function to mild renal impairment. 5 (6.0%) and 3 (3.6%) patients, respectively, shifted from mild renal impairment to moderate renal impairment.

The percentage of patients with ≥1 TEAE, ≥1 treatment-emergent AESI, and ≥1 treatment-related TEAE was similar between the normal renal function and mild renal impairment groups (Table 54). The percentage of ≥1 SAEs and ≥1 TEAE of CTCAE severity Grade ≥3 were slightly higher in the mild renal impairment group compared to the normal renal impairment group. Overall, it can be concluded that mild renal impairment does not appear to affect the overall tolerability profile of efgartigimod. It is confirmed that no clear pattern in the reported serious TEAEs and TEAEs of CTCAE severity Grade ≥3 is observed, which however, is not necessarily expected either. An overall increased exposure could lead

to more TEAEs overall without being restricted to single PTs. Of note, in the pop PK model, a statistically significant reduction in clearance with decreasing renal function (eGFR) was identified and a corresponding increase in AUC0-168h (28%; 90% confidence interval [CI]: 19% to 37%) after the fourth infusion was also reported. It is reassuring that no PT of neither serious TEAEs nor TEAEs of CTCAE severity Grade ≥3 were reported in >1 patient. Information on the limited safety and efficacy data in patients with renal impairment is appropriately reflected in section 4.2 of the SmPC. CHMP considered that no dose adjustment is required for patients with mild renal impairment since it can be concluded that mild renal impairment does not appear to affect the overall tolerability profile of efgartigimod.

In the moderate renal impairment group, the percentage of patients with ≥1 SAE, ≥1 TEAE of CTCAE severity Grade ≥3, ≥1 related TEAE, and ≥1 TEAE leading to interruption of IMP, were slightly higher than that of normal renal function and mild renal impairment groups. As the numbers for moderate (n=6) and severe (n=0) renal impairment are very low (or non-existing), no conclusion can be made on these patients.

Sufficient information regarding patients with renal impairment is included in the SmPC (sections 4.2 and 5.2.)

Table 54 – Overview of adverse events in the total efgartigimod group during all cycles cumulatively in pooling block 2, by estimated glomerular filtration rate value of baseline (safety analysis set)

Overall	Total Efgartigimod, All Cycles Cumulatively (N=162)					
	Normal Renal Function[a] (N=103)		Mild Renal Impairment[b] (N=53)		Moderate Renal Impairment[c] (N=6)	
	n (%)	m	n (%)	m	n (%)	m
≥1 TEAE	87 (84.5)	550	45 (84.9)	298	4 (66.7)	36
≥1 SAE	13 (12.6)	20	10 (18.9)	16	2 (33.3)	3
≥1 TEAE of CTCAE severity grade ≥3	18 (17.5)	40	12 (22.6)	21	2 (33.3)	6
≥1 Fatal TEAE	3 (2.9)	3	2 (3.8)	2	0	0
≥1 Related TEAE[d]	40 (38.8)	151	20 (37.7)	75	3 (50.0)	7
≥1 Related SAE[d]	0	0	1 (1.9)	1	0	0
≥1 TEAE leading to interruption of IMP	11 (10.7)	15	4 (7.5)	6	1 (16.7)	2
≥1 TEAE leading to discontinuation of IMP	6 (5.8)	11	5 (9.4)	6	0	0
≥1 AESI[e]	57 (55.3)	106	30 (56.6)	66	3 (50.0)	7
≥1 IRR[f]	10 (9.7)	12	3 (5.7)	4	0	0

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.1.7

AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; eGFR=estimated glomerular filtration rate; IMP=investigational medicinal product; IRR=infusion-related reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per treatment; PI=principal investigator; SMQ=standardized MedDRA queries TEAE=treatment-emergent adverse event

[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 but <90 mL/min/1.73m^2.

[c] Moderate renal impairment is defined as eGFR value that is ≥30 mL/min/1.73 m^2 but <60 mL/min/1.73m^2.

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

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

[f] IRRs were defined as adverse events within the SMQ (broad selection) for hypersensitivity, anaphylactic reaction, or extravasation events (excluding implants) and occurring within 48 h of an infusion, or within 2 days in case no start time was available.

Geographic Region

In PB1 and PB2, in the efgartigimod and placebo groups, a higher percentage of patients from the US had ≥1 TEAE or ≥1 TEAE considered by the investigator to be related to IMP compared to patients from the ROW. However, no clinically meaningful differences were observed by region because the frequency of these events was similar between the placebo and efgartigimod groups. Further, review of TEAE data by SOC suggested no additional safety issues by region.

Pregnancy and lactation

No clinical data have been collected on the safety of efgartigimod alfa in pregnancy and during lactation. The use in pregnant women has been included in the Risk Management Plan as missing information; the use in lactating women should be monitored through routine pharmacovigilance activities.

The following information has been reflected in the SmPC: *"As efgartigimod alfa is expected to reduce maternal antibody levels and is also expected to inhibit the transfer of maternal antibodies to the foetus, reduction in passive protection to the newborn is anticipated. Therefore, risks and benefits of administering live / live-attenuated vaccines to infants exposed to efgartigimod in utero should be considered (see section 4.4). Treatment of pregnant women with efgartigimod should only be considered if the clinical benefit outweighs the risks."*.

With regard to breastfeeding women, the SmPC states that "*There is no information regarding the presence of efgartigimod alfa in human milk, the effects on the breastfed child or the effects on milk production. Animal studies on the transfer of efgartigimod alfa into milk have not been conducted, and therefore, excretion into maternal milk cannot be excluded. Maternal IgG is known to be present in human milk. Treatment of lactating women with efgartigimod alfa should only be considered if the clinical benefit outweighs the risks."*

2.6.8.7. Immunological events

ADA

An integrated analysis of the immunogenicity data in efgartigimod clinical studies in patients with gMG was performed. This analysis includes studies ARGX-113-1704, ARGX-113-1705 (interim analysis with a cut-off date of 01 February 2021), and ARGX-113-1602. The patient population discussed in this integrated analysis is the safety population (i.e., all patients with gMG who received at least one dose or part of a dose of efgartigimod).

The ADA patient classification, incidence, and prevalence calculated on the pooled immunogenicity dataset of patients with gMG in studies ARGX-113-1704, ARGX-113-1705 (interim analysis) and ARGX-113-1602) are summarised in Table 55. Similar results were found for the AChR-Ab seropositive patients as compared to the overall population. Therefore, the description of the results in the following sections is focused on the overall population.

Table 55 – ADA patient classification, incidence, and prevalence over all cycles in the pooled immunogenicity data of studies ARGX-113-1704, ARGX-113-1705, and ARGX-113-1602

	Total Efgartigimod (N=162) n (%)
ADA Evaluable Patients	161 (99.4)
ADA Unevaluable Patients	1 (0.6)
Baseline ADA Sample Status (SEB)	
Sample Negative for ADA	129 (80.1)
Sample Positive for ADA	32 (19.9)
Overall ADA Subject Classification	
ADA Negative	130 (80.7)
ADA Negative	100 (62.1)
Treatment-Unaffected ADA	30 (18.6)
ADA Positive	31 (19.3)
Treatment-Induced ADA	29 (18.0)
Treatment-Boosted ADA	2 (1.2)
Incidence/Prevalence	
ADA Incidence	31 (19.3)
ADA Prevalence	61 (37.9)

Source: Table 14.2.5.2.5
ADA=anti-drug antibody; N=number of patients in the analysis set; n=number of patients for whom the observation was reported; SEB=study entry baseline

The ADA incidence in the total efgartigimod population was 19.3% and the ADA prevalence was 37.9%.

NAb

The NAb subject classification, incidence, and prevalence calculated on the pooled immunogenicity dataset of patients with gMG in studies ARGX-113-1704 and ARGX-113-1705 (interim analysis with 01 February 2021 data cut-off date) are summarised in Table 56. Similar results were found for the AChR-Ab seropositive population when compared to the overall population.

The majority of the patients (142 out of 150; 95.3%) were NAb negative, of which 140 (140/150; 94.0%) were classified as "NAb baseline negative – post-baseline negative" and 2 (2/150; 1.3%) were classified as "NAb baseline positive – post-baseline negative". There were 7 (7/150; 4.7%) patients who were NAb positive and classified as "NAb baseline negative – post-baseline positive". No patients were NAb positive at both baseline and post-baseline sampling timepoints.

The NAb incidence was 4.7% in the total efgartigimod treatment group and the NAb prevalence was 6.0%.

Table 56 – Nab patient classification, incidence, and prevalence (over all cycles) in the pooled immunogenicity data of studies ARGX-113-1704, ARGX-113-1705

	Efgartigimod (N=150[a]) n (%)
NAb evaluable patients	149 (99.3)
NAb unevaluable patients	1 (0.7)
Baseline NAb sample status	
NAb positive	2 (1.3)
NAb negative	147 (98.7)
NAb subject classification	
NAb positive	7 (4.7)
Baseline negative – postbaseline positive	7 (4.7)
Baseline positive – postbaseline positive	0
NAb negative	142 (95.3)
Baseline negative – postbaseline negative	140 (94.0)
Baseline positive– postbaseline negative	2 (1.3)
Incidence / prevalence	
NAb incidence	7 (4.7)
NAb prevalence	9 (6.0)

Source: Table 14.2.7.2.3
N=number of patients in the analysis set; n=number of patients for whom the observation was reported;
NAb=neutralizing antibody
[a] NAb evaluation was not performed for the 12 efgartigimod-treated patients in study ARGX-113-1602.

Impact of ADA and NAb on Safety

Overall, TEAEs were reported in 107 (107/161; 66.5%) patients in C1; in 68 (68/104; 65.4%) patients who were ADA negative, 20 (20/31; 64.5%) patients with treatment-unaffected ADA, 18 (18/25; 72%) patients with treatment-induced ADA, and 1 (1/1; 100%) patient with treatment-boosted ADA. No difference in overall TEAE profile between the ADA negative patients and patients with treatment-induced, treatment-boosted, or treatment-unaffected ADA was observed over the cycles examined.

No drug hypersensitivity or anaphylactic reactions were reported in the 29 patients who developed treatment-induced ADA, in the 30 patients with treatment-unaffected ADA, or in the 2 patients with treatment-boosted ADA).

In patients evaluated for NAb, TEAEs were reported in 97 patients in C1, in 94 NAb negative patients ('baseline negative-post-baseline negative' or 'baseline positive – post-baseline negative'), and in 3 NAb positive patients ('baseline-neg – post-baseline positive').

SAEs were reported in 3 patients (1 thrombocytosis, 1 vulval cancer and 1 acute myocardial infarction) with positive ADA, a causal relationship between the ADA development and the observed SAEs was considered unlikely by the Applicant. No SAEs occurred in NAb positive patients. In the integrated analysis including all efgartigimod studies in gMG, there was no apparent impact of pre-Ab, ADA, or NAb on the safety profile of efgartigimod. The pooled immunogenicity data does not raise any concerns regarding safety since the were no difference in the overall TEAE profile between the ADA positive and ADA negative patients and 3 SAEs are assessed unlikely to be related to ADA.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Clinical drug interactions studies have not been performed with efgartigimod, according to guideline (CHMP/EWP/89249/2004). Being a therapeutic protein with no expected cytochrome P450 or transporter involvement, the potential risk of PK interactions between efgartigimod and other drugs is low.

As of the data cut-off date of 01 February 2021, no TEAEs of drug interactions were reported at the PT level. 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 (Table 57).

Table 57 – Treatment-emergent adverse events of special interest reported in the total efgartigimod group that occurred during all cycles cumulatively in pooling block 2, by concomitant treatment for generalized Myasthenia Gravis, system organ class, and preferred term (safety analysis set)

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AESI[a]	15 (60.0)	24	16 (43.2)	31	9 (64.3)	19	50 (58.1)	105
Infections and infestations	15 (60.0)	24	16 (43.2)	31	9 (64.3)	19	50 (58.1)	105
Asymptomatic bacteriuria	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Bacteriuria	0	0	1 (2.7)	1	0	0	0	0
Body tinea	0	0	0	0	0	0	1 (1.2)	1
Bronchitis	1 (4.0)	1	2 (5.4)	3	0	0	5 (5.8)	7
Candida infection	0	0	0	0	0	0	1 (1.2)	1
Conjunctivitis	0	0	0	0	0	0	2 (2.3)	2
Coronavirus infection	0	0	0	0	0	0	1 (1.2)	1
COVID-19	2 (8.0)	2	0	0	1 (7.1)	1	3 (3.5)	3
COVID-19 pneumonia	0	0	0	0	0	0	2 (2.3)	2
Cystitis	0	0	1 (2.7)	2	0	0	2 (2.3)	2
Dysentery	0	0	0	0	0	0	1 (1.2)	1
Ear infection	0	0	0	0	1 (7.1)	1	1 (1.2)	1
Epididymitis	0	0	1 (2.7)	1	0	0	0	0
Fungal infection	0	0	1 (2.7)	1	0	0	0	0
Gastroenteritis	0	0	0	0	1 (7.1)	2	2 (2.3)	2
Gastroenteritis viral	1 (4.0)	1	1 (2.7)	1	0	0	0	0

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Gingivitis	0	0	0	0	1 (7.1)	1	2 (2.3)	2
Helicobacter infection	0	0	1 (2.7)	1	0	0	0	0
Herpes zoster	0	0	0	0	1 (7.1)	1	5 (5.8)	5
Hordeolum	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Influenza	1 (4.0)	1	1 (2.7)	1	0	0	3 (3.5)	3
Mastitis	0	0	0	0	1 (7.1)	1	0	0
Nail bed infection	0	0	0	0	0	0	1 (1.2)	1
Nasopharyngitis	6 (24.0)	7	3 (8.1)	4	2 (14.3)	4	13 (15.1)	17
Oral candidiasis	0	0	0	0	0	0	1 (1.2)	1
Oral herpes	0	0	0	0	1 (7.1)	1	3 (3.5)	3
Oropharyngeal candidiasis	0	0	1 (2.7)	1	0	0	0	0
Pharyngitis	2 (8.0)	2	1 (2.7)	1	0	0	1 (1.2)	1
Pharyngitis streptococcal	0	0	0	0	0	0	2 (2.3)	2
Pneumonia	0	0	1 (2.7)	1	0	0	2 (2.3)	2
Pneumonia escherichia	1 (4.0)	1	0	0	0	0	0	0
Pyelonephritis chronic	0	0	0	0	0	0	1 (1.2)	1
Respiratory tract infection	0	0	0	0	0	0	4 (4.7)	4
Respiratory tract infection viral	0	0	0	0	0	0	1 (1.2)	1
Rhinitis	0	0	0	0	0	0	1 (1.2)	1
Rotavirus infection	0	0	0	0	0	0	1 (1.2)	1

System Organ Class Preferred Term	Total Efgartigimod							
	No ST/NSID (N=25)		ST (N=37)		NSID (N=14)		ST+NSID (N=86)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Septic shock	0	0	0	0	0	0	1 (1.2)	1
Sialoadenitis	0	0	0	0	0	0	1 (1.2)	1
Sinusitis	0	0	0	0	2 (14.3)	2	1 (1.2)	1
Skin infection	0	0	1 (2.7)	2	0	0	1 (1.2)	2
Suspected COVID-19	1 (4.0)	1	0	0	0	0	0	0
Tinea versicolour	0	0	0	0	0	0	2 (2.3)	2
Tonsillitis	0	0	0	0	0	0	1 (1.2)	1
Tracheitis	0	0	0	0	0	0	2 (2.3)	2
Upper respiratory tract infection	3 (12.0)	4	2 (5.4)	2	1 (7.1)	2	6 (7.0)	9
Urinary tract infection	3 (12.0)	4	3 (8.1)	5	1 (7.1)	3	9 (10.5)	10
Viral infection	0	0	1 (2.7)	1	0	0	1 (1.2)	1
Viral pharyngitis	0	0	1 (2.7)	1	0	0	0	0
Viral tracheitis	0	0	0	0	0	0	1 (1.2)	1
Viral upper respiratory tract infection	0	0	0	0	0	0	2 (2.3)	2
Vulvovaginal candidiasis	0	0	0	0	0	0	1 (1.2)	1
Vulvovaginal mycotic infection	0	0	0	0	0	0	1 (1.2)	1

Source: Module 5.3.5.3, ARGX-113-9011-ISS, Table 14.3.1.2.9.2

AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients for whom the observation was reported; N=number of patients in the analysis set per standard of care category; PT=preferred term; SOC=system organ class; AESI=adverse event of special interest; NSID=nonsteroidal immunosuppressive drug; ST=steroids

Note: Adverse events were coded by SOC and PT using MedDRA version 23.0 (March 2020).

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

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). 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 has been included in the Risk Management Plan as missing information.

NSIDs or steroids were allowed and were extensively 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.

Vaccination

In studies ARGX-113-1704 and ARGX-113-1705, vaccination of patients 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.

PK and PD data show that, approximately 2 weeks after the last of 4 once weekly infusions of efgartigimod IV 10 mg/kg, IgG levels begin to increase. By that time, efgartigimod concentrations dropped to <2% of the Cmax. This indicates that 2 weeks after the last infusion, IgG catabolism is no longer meaningfully affected by efgartigimod and has returned to its normal rate.

Patients should not be vaccinated within 4 weeks of the initiation of efgartigimod treatment. For patients on efgartigimod treatment, vaccination with live or live attenuated vaccines is not recommended. However, other vaccines may be administered 2 weeks after the last infusion of a treatment cycle and 4 weeks before initiating the next treatment cycle.

The risk of interaction with vaccines is appropriately reflected in the SmPC sections 4.4 and 4.5.

2.6.8.9. Discontinuation due to adverse events

In study ARGX-113-1704, TEAEs that led to treatment discontinuation occurred in 3 (3.6%) patients in each treatment group. No TEAE that led to discontinuation was reported in more than 1 patient in either treatment group.

In study ARGX-113-1705, TEAEs that led to discontinuation of efgartigimod treatment occurred in 8 (5.8%) patients in the total efgartigimod group: 6 (8.2%) patients in the efgartigimod-efgartigimod cohort and 2 (3.0%) patients in the placebo-efgartigimod cohort. The TEAEs that led to discontinuation of efgartigimod reported in more than 1 patient in either cohort were myasthenia gravis and COVID-19 pneumonia, which were reported in the efgartigimod-efgartigimod cohort.

The following PTs reported in 6 patients were serious: spinal compression fracture, myasthenia gravis, lung neoplasm malignant, COVID-19 pneumonia, adenocarcinoma of colon, and acute myocardial infarction.

Two TEAEs of myalgia and headache in 1 patient that led to efgartigimod discontinuation were determined by the investigator to be possibly related to efgartigimod treatment.

In PB2, 11 (6,8%) TEAEs resulted in discontinuation. The profiles of TEAEs that led to IMP discontinuation were similar to the two studies ARGX-113-1704 and ARGX-113-1705.

The discontinuation data supports the observations from overall AEs.

Overdose, Drug abuse, Withdrawal and Rebound

The recommended dose of efgartigimod is 10 mg/kg as a 1-hour intravenous infusion. Seven patients received an efgartigimod dose >10% of the amount planned in the protocol. Four (4; 57.1%) of the 7 patients reported at least 1 TEAE (2 patients reporting 2 TEAEs, 2 patients reporting 5 TEAEs) however, the majority of the TEAEs were most likely not related to study drug and it is reassuring that the majority (12/15; 80.0%) of the reported TEAEs were reported as CTCAE Grade 1.

In the Phase 1 study ARGX-113-1501, TEAEs were reported in 3 (75,0%) patients receiving 25 mg/kg efgartigimod and in 4 (100,0%) patients receiving 50 mg/kg efgartigimod. The reported TEAEs were differential white blood cell count abnormal, CRP increased, headache, dizziness and chills.

2.6.8.10. Post marketing experience

Not applicable. Efgartigimod is not marketed in any country.

2.6.9. Discussion on clinical safety

Safety data

With regard to the safety exposure, the clinical safety database is based on two Phase 1 studies in adult subjects (ARGX-113-1501 and ARGX-113-1702), three clinical studies in adult patients with gMG (ARGX-113-1602, ARGX-113-1704 and ongoing study ARGX-113-1705) and one supportive study in adult patients with primary ITP (ARGX-113-1603). As the controlled clinical studies were all placebo-controlled studies, there are no data comparing the safety of efgartigimod with other medicinal products licensed for the treatment of Myasthenia Gravis (e.g. pyridostigmine and neostigmine), immunosuppressants (e.g. prednisone) and therapy with monoclonal antibody (e.g. eculizumab). NSIDs or steroids were allowed and were extensively 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 therapies allowed in pivotal trial are identified.

Overall, the safety database consists of a total of 143 patients treated with efgartigimod for at least 6 months, a total of 118 patients treated with efgartigimod for at least 12 months but only 33 patients treated for a least 18 months and one patient treated for at least 2 years. Despite the low prevalence of the disease (approximately 15-20 per 100.000), the safety database is considered small and rare events are not expected to be captured with the current safety database. In addition, long-term safety data beyond 2 years of exposure is extremely limited, which is a drawback in such a chronic indication. However, a PASS will be conducted with the aim to further characterize the identified and potential risks, missing safety-related information (long-term safety) and to detect specific and/or unexpected patterns of adverse events.

The safety data assessment is based on the following patients: *"the duration of treatment combined with follow-up was at least 6 months for 143 patients, at least 12 months for 118 patients, and at least 18 to <24 months for 33 patients. A total of 183.6 patient-years of follow-up have been collected as of 01 Feb*

2021 in gMG patients treated with efgartigimod." Considered the overall low prevalence of myasthenia gravis ('orphan disease') this is considered acceptable. Furthermore, for the ARGX-113-1705 interim analysis #3 cut-off date of 01 Feb 2021 and 22 Sep 2021, a total of 13 SAEs were reported in 10 patients.

In this period, the most commonly reported SAEs were COVID-19 (3 patients) and myasthenia gravis (2 patients). The 3 cases of Covid-19 could be due to a compromised immune system however, considered the Covid-19 pandemic (high frequency) this cannot be confirmed and as such 'Serious infections' have been included as an important potential risk in the RMP. 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.

Several exclusion criteria were applied and a discussion of how the applied exclusion criteria have potentially impacted the safety data was presented. Adequate information is included in section 5.1 of the SmPC.

With regard to the future plans for ensuring continuous safety data, a PASS will be conducted with the aim to further characterize the identified and potential risks, missing safety-related information and to detect specific and/or unexpected patterns of adverse events.

Adverse events

In all studies, the majority (>75%) of all (both placebo-treated and efgartigimod-treated) patients experienced ≥1 TEAE.

Overall, in the pivotal Phase 3 study ARGX-113-1704, slightly more patients treated with placebo compared to efgartigimod experienced ≥1 TEAE (84.3% placebo vs. 77.4% efgartigimod). The majority of TEAEs were of mild or moderate severity. TEAEs of CTCAE severity grade ≥3 were reported in similar percentages of patients in the efgartigimod and placebo groups (10.7% and 9.6%, respectively). TEAEs that were considered by the investigator to be related to treatment occurred with similar patient frequency between the treatment groups: 31.0% in the efgartigimod group and 26.5% in the placebo group. Headache (28.6% vs 27.7% of patients treated with efgartigimod and placebo, respectively), nasopharyngitis (11.9% vs 18.1%), upper respiratory infection (10.7% vs 4.8%), urinary tract infection (9.5% vs 4.8%) and nausea (8.3% vs 10.8%) were the most frequently reported AEs in the efgartigimod group. From these data, it seems that the underlying condition is contributing to a high extent to the overall reporting of AEs in both treatment arms.

On the contrary, more patients treated with efgartigimod experienced ≥1 AESI (MedDRA SOC infections and infestations) (46.4% efgartigimod vs. 37.3% placebo) and also more treatment-related TEAEs (31.0% efgartigimod vs. 26.5% placebo). This is expected since the mechanism of action of efgartigimod results in the reduction of total IgG and IgG subtypes.

In study ARGX-113-1705, the majority of patients reported ≥1 AE within the following SOCs: Infections and infestations (46.8% of all Efgartigimod patients), Nervous system disorders (35.3%), and Gastrointestinal disorders (29.9%). The most common PTs reported in ≥5% of all efgartigimod patients were Headache (22.3%), Diarrhoea (8.6%), Nasopharyngitis (10.8%), Urinary tract infection (7.2%), Oropharyngeal pain (5%), Arthralgia (5%), Nausea (5%), and Pyrexia (5%). In study ARGX-113-1704, Procedural headache was reported in 4 (4.8%) of the efgartigimod-treated patients. Headache was reported in 24 (28.6%) of the efgartigimod-treated patients.

An overview of TEAEs with efgartigimod over cycles showed a tendency towards more TEAEs and also more treatment-related TEAEs during the initial cycles compared to the later cycles. This may reflect that AEs are most pronounced in the beginning of the treatment, though it cannot be excluded that in some patients the TEAEs have let to study drug discontinuation early in the treatment period. Also TEAEs of severity grade ≥3 occurred in a comparable frequency between the efgartigimod and the placebo

group (Study ARGX-113-1704: 10.7% (efgartigimod) vs. 9.6% (placebo); Study ARGX-113-1705: 20.5% in the efgartigimod-efgartigimod cohort and 16.7% in the placebo-efgartigimod cohort). The higher frequency of severe TEAEs observed in Study ARGX-113-1705 may reflect a longer observation time in this study.

Fatal events were reported in 5 (3.1%) patients in the total efgartigimod group. None of the fatal events were considered by the investigator to be related to efgartigimod treatment (please see later section).

Common Adverse Events

The most frequently (≥10% in total efgartigimod group) reported PTs were headache (22.3%), and nasopharyngitis (10.8%). In study ARGX-113-1704, Procedural headache was reported in 4 patients, 4.8% of the efgartigimod-treated patients and Headache was reported in 24 patients, 28.6% of the efgartigimod-treated patients. It was clarified that the terms "headache occurring after each infusion and lasting until next day", "headache after IP administration" and "mild headache at day of last infusion" have been categorized as 'Procedural headache'; this has been appropriately reflected in section 4.8 of the SmPC.

As cardiac disorders (7.2% vs. 4.8% in the Total efgartigimod and the placebo groups, respectively), neoplasms (5.0% vs. 1.2% in the Total efgartigimod and the placebo groups, respectively) and renal and urinary disorders (4.3% vs. 1.2% in the Total efgartigimod and the placebo groups, respectively) were reported more frequently in the efgartigimod treatment group, it was discussed whether the mechanism of efgartigimod could lead to cardiac disorders and/or neoplasms and/or renal and urinary disorders, and if these AEs should be mentioned in the SmPC. With regard to cardiac disorders, there is no indication that Efgartigimod's method of action impacts the cardiac function and non-clinical data showed no cardiovascular system toxicities. In study ARGX-113-1704, in the SOC Cardiac disorders, TEAEs occurred at a higher frequency in the placebo group compared to the efgartigimod group. In study ARGX-113-1705, TEAEs in the SOC Cardiac disorders occurred with similar frequencies reported in the efgartigimod-efgartigimod and placebo-efgartigimod cohorts. Further, in the SOC Cardiac disorders the majority of TEAEs were assessed by the Investigator as not related or unlikely related to efgartigimod. In conclusion, there is no indication that the mechanism of efgartigimod could lead to cardiac disorders and it is considered acceptable not to mention the AEs in the SmPC.

With regard to malignancies the safety data reported in the efgartigimod studies in MG patients and available data for other IgG reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing cancer. However, malignancies have been included as an Important Potential Risk in the RMP.

Across the studies, the most commonly reported PT AEs were within the SOC Infections and infestations with the most commonly reported PTs being Upper Respiratory Tract Infections, Bronchitis, Urinary tract infections but also Ear infections and Gastroenteritis were reported more commonly in the efgartigimod group. Considering the biological plausibility due to efgartigimod's mechanism of action, a paragraph with information regarding the overall increased risk of infections as well as the most frequent reported infections has been included in section 4.8 of the SmPC.

Regarding the preferred terms that occurred at >1% higher frequency in the efgartigimod group than placebo in study ARGX-113-1704, these preferred terms were reviewed, and it is concluded that none should be considered associated with efgartigimod administration. With the exception of ear infection and sinusitis, all other infections were observed in a single patient, and therefore no conclusion can be drawn. Ear infection and sinusitis occurred at a >2% higher frequency in the efgartigimod group than placebo but were considered not related to efgartigimod by the investigator and therefore not considered an adverse drug reaction.

Three preferred terms were considered related to efgartigimod treatment by the investigator: nail-bed infection, influenza and pharyngitis. Nail-bed infection occurred in only 1 patient in both studies; therefore, no conclusion can be made. Influenza was reported in a higher proportion of patients in the placebo group versus the efgartigimod group and a similar frequency in the total efgartigimod group in study ARGX-113-1705 which includes a longer exposure period. Pharyngitis was reported in 1 patient; therefore, no conclusion can be made. It is considered that there is no sufficient evidence to support a causal relationship between the administration of efgartigimod and nail-bed infection, influenza, or pharyngitis.

An analysis of the temporary relationship among the 37 patients who reported both 'Lymphocyte count decreased' and 'Infections and infestation' as adverse events, showed no correlation and in the majority of patients reporting 'Lymphocyte count decreased', the lymphocyte count was still 500 to 800/microL. Therefore, it is concluded that there is no relation between 'Lymphocyte count decreased' and ATEAEs within the SOC 'Infections and infestation'.

Taken together, the adverse drug reactions listed in the SmPC section 4.8 were identified based on safety data from the double-blind, placebo-controlled study ARGX-113-1704. PTs that were reported in ≥4.8% of patients and with a higher occurrence in the efgartigimod group (≥ 3 [3.6%]) than in the placebo group were defined as ADRs. The following were identified as ADRs: bronchitis (6.0% vs 2.4%), upper respiratory tract infection (10.7% vs 4.8%), urinary tract infection (9.5% vs 4.8%), procedural headache (4.8% vs 1.2%) and myalgia (6.0% vs 1.2%). All ADRs were mild to moderate in severity, except for one event each of procedural headache and myalgia that were severe (CTCAE grade 3). Review of TEAE data from study ARGX-113-1705 (data cut-off 01 February 2021) and PB1, PB2, and PB3 did not identify additional ADRs or a clinically meaningful increase in the frequency of the ADRs identified in study ARGX-113-1704.

No additional safety issues were identified with prolonged and repeated administration of efgartigimod in Pooling Block 2. This is expected since TEAEs in general decreased in subsequent cycles.

The criteria for the selection of adverse reactions included in SmPC section 4.8 have been sufficiently justified.

There was no clear pattern of TEAEs or SAEs between the two patient populations (AChR-Ab seropositive and AChR-Ab seronegative patients). It was noted that all but one of the patients reporting myasthenia gravis crisis were AChR-Ab positive (5/6 ≈83%). This may (partly) be due to the higher frequency (80%) of AChR-Ab seropositive included in the study. However, in a study by Malik YM. et al. (Malik YM, Dar JA, Almadani AA (2019) Role of Myasthenia Gravis Auto-Antibodies as Predictor of Myasthenic Crisis and Clinical Parameters. J Neurol Neurosci Vol.10 No.1:281) it was found that *"In terms of Immunology 67% of AchR-Ab positive patients, all of MuSK-Ab positive and only 33% of seronegative patients underwent crisis, hence crisis occurred predominantly in seropositive myasthenia (p<0.05)."* and also: *"Seropositive MG patients had about 30% more tendency to develop crisis (p=0.019), especially patients with MuSK-Ab MG had more frequent crisis, however there was no statistically significant relationship between severity of crisis with any particular antibodies."* Either way, the indication has been restricted only to include AChR-Ab seropositive patients (*"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."*) and the finding that myasthenia crisis may be more common in this patient population (compared to the AChR-Ab seronegative patients) does not alter the benefit-risk assessment.

Serious adverse events and deaths

Serious adverse events

In study ARGX-113-1704, treatment-emergent SAEs occurred in 4.8% of the patients in the efgartigimod group and 8.4% in the placebo group. No treatment-emergent SAE was reported in greater than 2 patients in either treatment group.

In study ARGX-113-1705, treatment-emergent SAEs occurred in 21 (15.1%) patients of the total efgartigimod group with almost twice as high frequency in the efgartigimod-efgartigimod cohort compared to the placebo-efgartigimod cohort (19.2% vs 10.6%). Reassuringly, an overview of serious TEAEs by cycle in study ARGX-113-1705 has been presented, showing that the majority of the serious TEAEs occurred in the efgartigimod-efgartigimod cohort during Cycle 1 (in which patients had already received 1, 2 or 3 cycles of treatment with efgartigimod in antecedent study ARGX-113-1704) and that the imbalance in the number of serious TEAEs was not observed in subsequent treatment cycles.

The most commonly reported treatment-emergent SAEs (>3 patients) in the total efgartigimod cohort were within the SOCs of Infections and Infestations (6 patients [4.3%]), Nervous System Disorders (5 patients [3.6%]), and Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps) (4 patients [2.9%]). None of these SAEs were assessed by the Investigator to be treatment-related. However, considered the mechanism of action with efgartigimod reducing the level of IgG, it is indeed considered likely that the efgartigimod does affect the immune system and that efgartigimod treated patients have an increased risk of infections and infestations. As such, a warning has been included in section 4.4 of the SmPC to warn prescribers about the risks of administrating Vyvgart to patients with an active infection.

As 6 serious TEAEs in the SOC Neoplasms Benign, Malignant and Unspecified were reported in 5 patients in the Efgartigimod treatment group (vs. none in the placebo group), the Applicant discussed if the cases could be treatment-related. An overview of the neoplasm events, analysis of the events by treatment cycle and onset latency was provided as well as an overview of other anti-FcRn biologics under development and their relatedness to neoplasms.

The safety data reported in the efgartigimod studies in MG patients and available data on other IgG reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing cancer. However, even though a correlation could not be found, it is noteworthy that 11 events have been reported in efgartigimod treated patients and only one case in the placebo group. Malignancies have been included as an Important Potential Risk in the RMP.

Deaths

A total of 5 fatal cases were reported in the efgartigimod cohorts and none in the placebo cohorts. 2 cases of death were associated with SAE of cardiovascular disease, 1 case was related to lung cancer, 1 case was due to myasthenia crisis and 1 case was due to infections (covid-19, pneumonia, UTI and septic shock).

Adverse events of special interest

In study ARGX-113-1704, 46.4% of the patients in the efgartigimod group and 37.3% of the patients in the placebo group reported treatment-emergent AESIs. The most frequently reported treatment-emergent AESIs in the overall population were: Nasopharyngitis, Upper respiratory tract infection, Urine tract infections and Bronchitis. Except for nasopharyngitis, all AESIs in the overall population were reported more frequently in the efgartigimod group compared to the placebo group.

Infections

As expected, efgartigimod treatment is associated with an increased frequency of infections. The decrease of IgG levels due to the pharmacological action of efgartigimod, may have an influence on the patients being more prone to infections. In particular, herpes viral infections, candidiasis and vulvovaginal mycotic infection were only reported in efgartigimod-treated subjects during the clinical

development. From the 12 efgartigimod-treated patients who had a herpes or candidiasis-relevant infection, 11 were receiving concomitant immunosuppressives (corticosteroids and/or azathioprine and/or mycophenolate mofetil), which are associated with a high risk of opportunistic infections. However, concomitant use of immunosuppressant treatments for gMG did not appear to increase the overall risk of infections, which is reassuring. Furthermore, literature has been provided to support that FcRn is less likely associated with increased infection risk or opportunistic infections when compared with steroids or other immunosuppressants. Section 4.4 of the SmPC, provides adequate and sufficient information regarding the precautions to be considered in case of an active infection at time of administration of efgartigimod.

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.

Laboratory values

Overall, there were no clinically relevant changes in laboratory values. Lymphocyte count decreased in 8 (9.5%) patients in the efgartigimod group and 8 (9.6%) patients in the placebo group in study ARG-113-1704, and in 13 (9.4%) patients in the total efgartigimod cohort in study ARG-113-1705. There is no indication, that Lymphocyte count decreased was associated with an increased risk of infections.

Information regarding hepatic enzymes and parameters (alanine aminotransferase, aspartate aminotransferase and bilirubin) is sparse. No patients fulfilled the criteria for Hy's law i.e. no patients experienced alanine aminotransferase or aspartate aminotransferase increases ≥3 times upper limit of normal and a total bilirubin ≥2 times upper limit of normal.

Few patients experienced an increase in cholesterol and/or hypertriglyceridemia. An evaluation of the laboratory abnormalities of high cholesterol and hypertriglyceridemia in the studies ARGX-113-1704 and ARGX-113-1705 was presented. In conclusion, no association with laboratory abnormalities of hypertriglyceridemia or high cholesterol and efgartigimod was found.

Vital signs and ECG

Vital signs

There were overall no notable changes from baseline in vital sign parameters (heart rate, systolic BP, and diastolic BP) or differences between the efgartigimod placebo cohort in study ARGX-113-1704, or differences between the efgartigimod-efgartigimod and placebo-efgartigimod cohorts in study ARGX-113-1705.

ECG

With regard to the imbalance of patients who had (a) a post-infusion QTcF interval measurement between >450 to ≤480 ms (10 (15.2%) patients in the placebo-efgartigimod treatment group vs. 4 (5.6%) patients in the efgartigimod-efgartigimod treatment group), and (b) a QTcF interval increase from baseline of [30,60] ms (21 (31.8%) patients in the placebo-efgartigimod treatment group vs. 11 (15.7%) patients in the efgartigimod-efgartigimod treatment group) in Study ARGX-113-1705, it was argued that the higher third quartile (Q3; 75th percentile) value in the placebo-efgartigimod cohort provides a potential explanation for the difference in the rates of worst abnormalities in the >450 to ≤480 ms range. Further analyses of the data have shown that 25% of the highest baseline QTcF values in the placebo-efgartigimod cohort were >421 ms, which was noticeable higher than observed in the efgartigimod-efgartigimod group (with the 25% of the highest baseline QTcF values being >414.0 ms).

Immunological events

In PB2 (i.e. based on data from Trials ARGX-113-1602, ARGX-113-1704 and ARGX-113-1705), 32 out of 161 (19.9%) patients with gMG had samples positive for ADA at baseline. While this could indicate that the specificity/selectivity of the screening and confirmation ADA assay is not adequate for assessment of the immune response of efgartigimod or that pre-existing antibodies are present, it was clarified that prevalence of pre-Abs against efgartigimod is simply rather high in both healthy subjects (between 10% and 32.5%) and MG patients (between 15.2% and 29.2%).

Overall, 29 out of 162 (18.0%) patients had a treatment-induced ADA response and 2 out of 162 (1.2%) patients had a treatment-boosted ADA response. The pooled immunogenicity data does not raise any concerns regarding safety since there were no differences in the overall TEAE profile between the ADA positive and the ADA negative patients.

Safety in special populations

Data for subgroups based on race, gender, age (</≥65 years), body weight and seropositive/sero-negative patients and patients with renal impairment were presented. Overall, patients ≥65 years seem to have more severe (grade ≥3) TEAEs (28.0% vs. 18.2%). Further data did not show any specific pattern and the reason is most likely due to the overall higher morbidity among elderly persons. With regard to gender, males reported substantially more severe (grade ≥3) TEAEs compared to the females (28.9% vs. 16.2%), but the number of patients in each subgroup is low and no conclusions can be made. Reassuringly, similar differences in TEAEs among genders were observed in the placebo group, and the issue will not be pursued.

Compared to patients with normal renal function, patients with mild and moderate renal impairment experienced slightly more severe (grade ≥3) TEAEs however, dose-reduction is not deemed necessary in patients with mild or moderate renal impairment. Information regarding posology and experience in renal impaired patients is sufficiently included in the SmPC (sections 4.2 and 5.2).

With regard to use of efgartigimod during pregnancy and lactation, no clinical data have been collected on the safety of efgartigimod in pregnancy and during lactation and hence, the use in pregnant has been included in the Risk Management Plan as missing information. This is appropriately reflected in section 4.6 of the SmPC.. A recommendation only to use efgartigimod during pregnancy and lactation if the clinical benefit outweighs the risks has also been included in the SmPC.

Discontinuations

In study ARGX-113-1704, TEAEs that led to treatment discontinuation occurred in 3 (3.6%) patients in each treatment group (placebo and efgartigimod). It is reassuring that no TEAE that led to discontinuation was reported in more than 1 patient in either treatment group.

Drug-drug interactions

There are no known drug-drug interactions with efgartigimod. NSIDs or steroids were allowed and were extensively used in the study populations; therefore, any potential interaction is accounted for in the safety profile.

The use of efgartigimod with monoclonal antibodies has been included in the Risk Management Plan as missing information; this is supported. Efgartigimod may decrease concentrations of compounds that bind to the human FcRn and may affect the safety and response to immunisation with vaccines; this has been reflected in the SmPC section 4.4.

The risk of interaction with vaccines has been sufficiently reflected in the SmPC (section 4.4 and 4.5).

Overdose, drug abuse, withdrawal

The recommended dose of efgartigimod is 10 mg/kg as a 1-hour intravenous infusion. Seven patients received an efgartigimod dose >10% of the amount planned in the protocol. The majority of the TEAEs reported in these patients are most likely not related to study drug and it is reassuring that the majority (12/15; 80.0%) of the reported TEAEs were reported as CTCAE Grade 1.

Section 4.9 of the SmPC sufficiently address the symptoms and management of (potential) overdose.

There is no data indicating withdrawal or rebound effect of efgartigimod. There is no obvious potential for drug abuse and considered the indication, the mechanism of action, the administration form as well as the effect and adverse effects of efgartigimod, there is no basis for drug abuse. The product will only be used in specific patients, administrated by healthcare professionals and in hospital settings. During the clinical studies no patients experienced rebound effect or signs of withdrawal. No additional safety issues were identified with prolonged and repeated administration of efgartigimod.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.10. Conclusions on the clinical safety

Overall, the safety database consists of a total of 143 patients treated with efgartigimod for at least 6 months, a total of 118 patients treated with efgartigimod for at least 12 months and only 33 patients treated for a least 18 months. In addition, only one patient has been followed-up for at least two years. Thus, the safety data is hampered by the few patients included, which is a drawback in such a chronic indication. However, a PASS will be conducted with the aim to further characterize the identified and potential risks, missing safety-related information (long-term safety) and to detect specific and/or unexpected patterns of adverse events.

Overall, available safety data from the clinical development program show that efgartigimod was generally well tolerated. Efgartigimod is considered to be associated with a higher risk of infections. In particular, herpes viral infections, candidiasis and vulvovaginal mycotic infection were only reported in efgartigimod-treated subjects during the clinical development. This is in accordance with its mechanism of action as a FcRn antagonist, which causes transient reduction in IgG levels. However, these risks are appropriately managed with the inclusion of warnings in the SmPC.

CHMP considered that the clinical safety data submitted supports the use of efgartigimod in the approved indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 58 - 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

Summary of safety concerns	
	Use with monoclonal antibodies Use in patients with moderate and severe renal impairment Long-term safety of efgartigimod treatment Use in immunocompromised patients

2.7.2. Pharmacovigilance plan

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 of adverse events.	• Long-term safety of efgartigimod treatment • Serious infections • Malignancies • Effect on vaccination efficacy and the use of live/attenuated vaccines • Use with monoclonal antibodies • Use in patients with moderate and severe renal impairment • Use in immunocompromised patients	Protocol submission	Within 3 months from the date of EC decision
			Interim report	Q4 2025
			Final report	Q1 2029

2.7.3. Risk minimisation measures

Table 59 - 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: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS - Q1 2029

Safety Concern	Risk Minimization Measures	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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17.12.2021.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group. The particulars to be omitted as per the QRD Group decision will however be included in the Annexes published with the EPAR on EMA website and translated in all languages, but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vyvgart (efgartigimod alfa) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication for efgartigimod is

"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 recommended dose schedule is 10 mg/kg (as a 1 hour intravenous infusion) to be administered in cycles of once weekly infusions for 4 weeks.

Generalised myasthenia gravis (gMG) 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 (NMJ), 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 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 or rituximab are used for more refractory cases.

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, the complement inhibitor eculizumab , and azathioprine , which have received regulatory approval for the treatment of gMG; 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 eculizumab is approved only for AChR-Ab seropositive patients and is limited to treatment of refractory MG. On the other hand, some subgroups usually greatly benefit from plasma exchange (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

The pivotal trial for this application is a single phase III multicentre, randomised, double-blind study aimed to show efficacy of 10 mg/kg efgartigimod intravenous (IV) administered in cycles of 4 once weekly infusions versus placebo in patients with gMG who had MG-ADL scores ≥5 points (with >50% of the score due to non-ocular symptoms) while receiving concomitant gMG treatment (study ARGX-113-1704).

3.2. Favourable effects

During the first treatment cycle in the AChR-Ab seropositive population, the MG-ADL responder criterion was met in 44 (67.7%) patients in the efgartigimod group compared to 19 (29.7%) patients in the placebo group, with an OR (95% CI) of 4.95 (2.21; 11.53) ($p<0.0001$).

The first three secondary endpoints (QMG Responders in the AChR-Ab Seropositive Population During Cycle 1, MG-ADL Responders in the Overall Population During Cycle 1 and, Percentage of Time of Clinically Meaningful Improvement in the AChR-Ab Seropositive Population) were also shown to have significant difference for efgartigimod in comparison to placebo.

Other scales or analysis of interest were MGC and Minimal Symptom Expression (an MG-ADL total score of 0 or 1) at week 4 of C1. The MGC score estimate at week 4 in the AChR-Ab seropositive population was −5.768 in the efgartigimod group compared to 0 in the placebo group. In the AChR-Ab seropositive population, an MG-ADL score of 0 or 1 was reported in 22.3% of patients in the efgartigimod group compared to 3.3% of patients in the placebo group at week 4 of C1.

Maximum improvement was observed at week 4; nominally significant differences from baseline observed from week 1 and sustained through week 7.

Preliminary results from long-term efficacy data provided by Study 1705, still ongoing are also supportive as well as the results from the exploratory Phase 2 study results conducted in seropositive patients

3.3. Uncertainties and limitations about favourable effects

The efficacy data assessment is based on a single 26-week, randomized, placebo-controlled phase 3 clinical trial with 65 efgartigimod and 64 placebo patients in the AChR-Ab seropositive population. The number of patients exposed, and the duration of the trial are limited and, there is no additional confirmatory phase 3 trial ongoing. However, this is considered acceptable due to rarity of the condition as a single well-conducted and adequately powered confirmatory trial showing results sufficiently compelling with respect to internal and external validity, clinical relevance, data quality, and internal consistency.

The results provided by the pivotal trial do not allow to conclude on the effect of the medicinal product on the global, broad gMG population. Primary endpoint and statistical analyses plan were designed to assess efficacy of efgartigimod in AChR-Ab seropositive population only. Also, secondary objectives are mainly focused in this subset. Results observed in seronegative population are concerning due to no difference between treatment arms on MG-ADL responders and very high placebo response (68.4% in the efgartigimod group and 63.2% in the placebo group). There were only six patients with anti-MUSK antibodies, three in each treatment group, and all six were MG-ADL responders in cycle 1. Other autoantibodies were not tested.

In the overall population MG-ADL responder criterion was met in 57 (67.9%) patients in the efgartigimod group compared to 31 (37.3%) patients in the placebo group [OR (95% CI) 3.70 (1.85; 7.58)]. These

figures compare to 67.7% vs. 29.7 [OR (95% CI) 4.951 (2.213, 11.5289); p-value <0.0001] in seropositive patients (primary analysis). The mean (SE) percentage of time patients reported having a Clinically Meaningful Improvement was 58.199% (5.465) in the efgartigimod group compared to 39.607% (5.441) in the placebo group (compared to 48.71% vs 26.65% in seropositive patients). The reduced magnitude of the effect observed in the global population with respect to the seropositive group and the lack of effect on seronegative patients suggests that results are mainly driven by the effect observed in the seropositive population.

Long term maintenance of effect is unknown and is not tested beyond 2 cycles of treatment in randomized controlled design. Maintenance of the effect is based also on preliminary data from Study ARGX-113-1705 with an intended duration of 3 years. Open label extension study presents data for patients who were treated up to 10 cycles, however, the numbers of patients treated are very low in longer term, so there are limitations to the maturity of data.

A sustained reduction of total IgG level was observed at 672 h (28 days) postdose after a 10 mg/kg single dose. As such, it is possible that a less frequent (more convenient) administration of efgartigimod could also achieve a similar effect.

Nearly all patients (93.4%) included in the pivotal study had at least 2 prior therapies, and 77.2% of patients had at least 3 prior therapies. During the study, approximately 70% of efgartigimod-treated patients were receiving steroids and 60% were receiving NSIDs. They represent a heavily treated population. The effect of efgartigimod as monotherapy has not been investigated and it is reflected in the approved indication as "add on" therapy.

The subgroup analysis showed no effect in the Japanese/Asian population (MG-ADL responder analysis 42.9% vs.42.9%). No relevant differences were observed in the PK analysis, apart from those related to body weight.

3.4. Unfavourable effects

The majority (84.0%) of all efgartigimod-treated patients experienced ≥1 TEAE and 15.4% of all efgartigimod-treated patients experienced ≥1 SAE. In study ARGX-113-1704, the most commonly reported AEs PTs in the efgartigimod group were: headache (28.6% vs 27.7% of patients treated with efgartigimod and placebo, respectively), nasopharyngitis (11.9% vs 18.1%), upper respiratory infection (10.7% vs 4.8%), urinary tract infection (9.5% vs 4.8%) and nausea (8.3% vs 10.8%) were the most frequently reported AEs in the efgartigimod group.

Across the clinical studies, the most commonly reported PT AEs were within the SOC Infections and infestations. Due to the mechanism of action for efgartigimod (reduction of the IgG level), patients may be considered more vulnerable for infections and infestations. Further, 9.5% of all efgartigimod-treated patients experienced 'Lymphocyte count decreased' however, data support, that there is no relation between 'Lymphocyte count decreased' and infections.

Procedural headache (reported when a headache was judged to be temporally related to the intravenous infusion of efgartigimod alfa) was reported in 4.8% of the efgartigimod-treated patients and Headache was reported in 28.6% of the efgartigimod-treated patients and 27.7% of the placebo-treated patients.

In study 1705, 31.8% (21 patients) in the placebo-efgartigimod group had a QTcF interval increase from baseline of [30,60] ms, compared to 15.7% (11 patients) in the efgartigimod-efgartigimod cohort. Post-infusion QTcF interval measurement between >450 to ≤480 ms were reported in 15.2% (10 patients) patients in the placebo-efgartigimod cohort compared to 5.6% (4 patients) patients in the efgartigimod-efgartigimod cohort. This difference has been explained by the higher third quartile (Q3; 75th percentile) value in the placebo-efgartigimod cohort and reassuringly, there is no excess in cardiovascular events.

Serious adverse events were reported in 15.4% of all efgartigimod treated patients; most commonly within the SOCs Infections and Infestations and Neoplasms (see uncertainties below). Only few SAEs were reported in ≥1 patient.

In conclusion, infections are a safety concern based on efgartigimod's mechanism of action and the high frequency of reported infections. Further, a substantial proportion of patients reported headache in relation to treatment with efgartigimod.

3.5. Uncertainties and limitations about unfavourable effects

The safety database consisting of a total of 143 patients treated with efgartigimod for at least 6 months, a total of 118 patients treated with efgartigimod for at least 12 months and only 33 patients treated for a least 18 month is, despite the low prevalence of the disease (approximately 15-20 per 100.000) is considered small. Rare events are not expected to be captured with the current safety database.

In addition, long-term safety data beyond 2 years of exposure is extremely limited, which is a drawback in such a chronic indication.

Efgartigimod is 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.

Fatal events were reported in 5 (3.1%) patients in the total efgartigimod group. None of the fatal events were considered by the investigator to be related to efgartigimod treatment, but one death was due to lung cancer. Though there is no clear mechanism of action, it is noted that as of the clinical cut-off date, overall, 11 events of neoplasms have been reported in efgartigimod-treated gMG patients at the intended dose (one in study ARGX-113-1704 and 10 in 7 patients in study ARGX-113-1705) and only one case has been reported in the placebo group. Of these, 6 events were considered serious in 5 efgartigimod-treated patients and none in placebo-treated patients. Since tumour-associated immunity typically involves IgG responses (Sharonov et al. B cells, plasma cells and antibody repertoires in the tumour microenvironment. Nat Rev Immunol. 2020 May;20(5):294-307) and an important role of FcRn in anti-tumour immune surveillance has been suggested (Baker et al. Neonatal Fc receptor expression in dendritic cells mediates protective immunity against colorectal cancer. Immunity. 2013 Dec 12;39(6):1095-107; Castaneda et al. Lack of FcRn Impairs Natural Killer Cell Development and Functions in the Tumor Microenvironment. Front Immunol. 2018 Sep 28;9:2259), the development of neoplasms and malignancies is another important potential risk in the context of a long-term treatment. Even though a correlation couldn't be found, it is noteworthy that 11 events have been reported in efgartigimod treated patients and only one case in the placebo group. Malignancies has been included as an Important Potential Risk in the RMP.

Six patients (4.3%) experienced 8 events in the SOC Renal and Urinary Disorders in the extension study ARGX-113-1705 compared to one patient (1.2%) among the placebo-treated patients. Given the protective role of FcRn in avoiding the accumulation of IgG and IgG immune complex in the kidney (Akilesh et al. Podocytes use FcRn to clear IgG from the glomerular basement membrane. Proc Natl Acad Sci U S A. 2008 Jan 22;105(3):967-72. Dylewski et al. Differential trafficking of albumin and IgG facilitated by the neonatal Fc receptor in podocytes *in vitro* and *in vivo*. PLoS One, 2019 Feb 27;14(2):e0209732.), inhibiting FcRn could be potentially harmful, especially in certain disease situations, such as, but not limited to, lupus nephritis and cryoglobulinemic glomerulonephritis. However, relevant literature suggesting the beneficial effect of systemic reduction of pathogenic immune complexes by FcRn blockade has been provided.

Safety data have been presented for different subgroups including age (patients <65 years and ≥65 years), gender, Race, geographical region, body weight, renal function and AChR-Ab seropositive/seronegative. More elderly patients (≥65 years) compared to the younger patients experienced AEs and likewise, the percentage of serious TEAEs and ≥1 TEAE of CTCAE severity Grade ≥3 were higher in the males (24,4% and 28.9%) compared to the females (12,0% and 16,2%). Of note, numbers in each subgroup is low and it is not expected that the observed differences are related to efgartigimod.

The uncertainty regarding the use of efgartigimod during pregnancy and breastfeeding is a matter of concern in a medicinal product that is intended for the long-term treatment of a disease that most commonly affects young adult women. A reduction in passive protection to the new-born due to the lowering of maternal antibody levels is anticipated if used in pregnant women and an immunosuppressive effect on the breasted child cannot be ruled out, both of which could expose the infant to a higher risk of infections. A recommendation only to use efgartigimod in pregnant and lactating women if the clinical benefit outweighs the risks is included in the SmPC. Further, the use in pregnant women has been included in the Risk Management Plan as missing information.

Formal drug-drug interaction studies have not been performed. There is currently no data regarding concomitant treatment with monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass). From the clinical Phase III studies, there is no indication of more AEs (including infections) when efgartigimod was administered concomitant with NSIDs or steroids, which are also used in the treatment of Myasthenia Gravis. Nevertheless, the concomitant use of efgartigimod with these products results in an additive immunosuppressive effect, affecting both humoral and cellular immunity, that might have unforeseen consequences in safety in the long-term.

Due to lack of experience, vaccination of patients with live or live attenuated vaccines is not recommended within 4 weeks prior to efgartigimod treatment, and vaccination with other vaccines is recommended to be at least 2 weeks after the last infusion of a treatment cycle and 4 weeks before initiating the next cycle. This is sufficiently addressed in the SmPC.

3.6. Effects Table

Table 60 - Effects Table for Vyvgart 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

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	MG-ADL Responders in AChR-Ab seropositive Population, mITT analysis set, during C1	Number of subjects	65	64	Maximum improvement at week 4; nominally significant differences from baseline observed from week 1 and sustained through week 7. Clinically meaningful change	
		n (%)	44 (67.7%)	19 (29.7%)		
		Odds Ratio (95% CI)	4.951 (2.213, 11.528) P<0.0001			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Secondary key endpoint 1	QMG responders in the AChR Ab seropositive population	Number of subjects	65	64	Maximum improvement at week 4; nominally significant differences from baseline observed from week 1 and sustained through week 7. Clinically meaningful change	
		n (%)	41 (63.1%)	9 (14.1%)		
		Odds Ratio (95% CI)	10.842 (4.179, 31.200) P<0.0001			
Secondary key endpoint 2	MG-ADL responders in overall population	Number of subjects	84	83	Maximum improvement at week 4; nominally significant differences from baseline observed from week 1 and sustained through week 7. Driven by only AChR-Ab seropositive group.	
		n (%)	57 (67.9%)	31 (37.3%)		
		Odds Ratio (95% CI)	3.699 (1.854, 7.578) P<0.0001			
Secondary key endpoint 3	Percentage of time that patients have a CMI in MG-ADL total score compared to SEB in AChR Ab seropositive patients	Number of subjects	65	64		
		LS mean (SE)	48.714 (6.163)	26.649 (6.316)	Difference: 22.065 (5.616) P value: 0.0001	
		95% CI	(36.517; 60.912)	(14.148; 39.151)	Difference: (10.949; 33.181)	
MGC	Change in the MGC score at week 4 in the AChR-Ab seropositive population	LS mean (SE)	−8.913 (0.974)	−2.871 (1.007)	nominal p<0.0001 Clinically relevant change on known and validated scale.	
Minimal Symptom Expression	MG-ADL total score of 0 or 1, observed at week 4 of C1, in AChR-Ab seropositive population	%	22.3%	3.3%	Important as general treatment goal for MG	
	MG-ADL total score of 0 or 1, observed anytime during C1, in AChR-Ab seropositive population	N (%)	26 (40%)	7 (11.1%)		
Unfavourable Effects						
≥TEAEs	Proportion	N (%)	136 (84%)	70 (84,3%)		PB2 and Study ARGX-113-1704

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
≥SAEs	Proportion	N (%)	25 (15,4%)	7 (8,4%)		PB2 and Study ARGX-113-1704
URTI PT AEs	Proportion	%	10.7%	4,8%		Study ARGX-113-1704
Bronchitis PT AEs	Proportion	%	6.0%	2,4%		Study ARGX-113-1704
UTI PT AEs	Proportion	%	9.5%	4,8%		Study ARGX-113-1704
Procedural headaches PT AEs	Proportion	%	4.8%	1,2%	Procedural headache and the difference between this and Headache is not clear	Study ARGX-113-1704
Headache PT AEs	Proportion	%	28,6%	27,7%		Study ARGX-113-1704
Myalgia PT AEs	Proportion	%	6.0%	1,2%		Study ARGX-113-1704
Lymfocyte count decreased CTCAE Grade 3	Proportion	%	9,5%	9,6%	Unclear if these events were associated with infections	Study ARGX-113-1704
Infections and infestations SOC AEs	Proportion	%	46,4%	37,3%		Study ARGX-113-1704
QTcF interval increase from baseline of [30,60] ms,	Proportion	%	15.7%	31.8%	No formal QTc study has been conducted, nor is such study planned.	Study ARGX-113-1705
QTcF interval measurement between >450 to ≤480 ms	Proportion	%	5.6%	15.2%		Study ARGX-113-1705
Death	Proportion	%	5 (3.1%)	0 (0%)		PB2 and Study ARGX-113-1704

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Treatment-induced ADA response	Proportion	%	18.0%		Clinical impact of ADA is currently unclear.	PB2
Treatment-boosted ADA response	Proportion	%	1.2%			PB2

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The approved indication for efgartigimod is *"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.".* Anti-AchR antibodies are primarily of the IgG1 and IgG3 isotypes, MuSK Abs are predominantly of the IgG4 isotype. Lrp4 antibody (to low-density lipoprotein-related receptor protein 4) is predominantly of the IgG1 isotype. Both seropositive and seronegative patients would have been candidates to be treated with efgartigimod since its mechanism of action results in the reduction of total IgG and IgG subtypes. However, in view of the available data, there was not enough evidence to support the use of Vyvgart in seronegative patients.

The recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient. Each treatment cycle consists of 4 infusions with an interval of at least 3 days apart.

The clinical pharmacology of efgartigimod is documented in two Phase 1 studies in healthy subjects and in a Phase 2 and a Phase 3 study in patients with gMG. 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 importantly, the clinical pharmacology and the Phase I clinical studies in healthy volunteers (Trials ARGX-113-1501 and ARGX-113-1702) support the proposed dosing of efgartigimod.

The clinical efficacy and safety of efgartigimod was primarily investigated in a single pivotal trial (Study ARGX-113-1704), in which 167 patients were enrolled, 152 (91.0%) patients completed treatment and 156 (93.4%) patients completed the study. Considered that gMG can be considered an orphan disease, the clinical data based on one single pivotal study is acceptable. Of note, no scientific advice was requested prior to or during the clinical trials. Overall, Study ARGX-113-1704 can be considered a well-performed trial according to recommended standards (a randomised, double-blind, placebo-controlled, parallel-group, multi-center study). The primary endpoint was reached and supported by first secondary endpoint on QMG. These results mean less functional disability as rated by patients and less disease severity as assessed by qualified physicians with statistically significant better effect compared to placebo. The effect had an early onset (as early as week 1) and is considered clinically relevant. Other secondary or exploratory endpoints supported the primary endpoint.

Importantly, the primary endpoint was based on AChR-Ab seropositive patients and thus, the study was not powered to find any statistically significant effect in the AChR-Ab seronegative patients alone. Effect

in the AChR-Ab seronegative patients was investigated as a secondary endpoint in Study ARGX-113-1704. No difference between treatment arms on MG-ADL responders was observed in AChR-Ab seronegative patients. Further, the long-term maintenance of effect of efgartigimod alfa is unknown as Study ARGX-113-1704 only included approximately two cycles of treatment for majority of the patients. Thus, maintenance of the effect is primarily based on preliminary data from the ongoing open-labelled extension Study ARGX-113-1705 with an intended duration of 3 years.

The safety database consisted of a total of 143 patients treated with efgartigimod for at least 6 months, a total of 118 patients treated with efgartigimod for at least 12 months and only 33 patients treated for a least 18 months.

Thus, rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the limited number of patients included. In addition, long-term safety data beyond 2 years is extremely limited, which is a drawback in such a chronic indication.

The majority (84%) of all efgartigimod-treated patients experienced ≥1 TEAE and approximately 15% of all efgartigimod-treated patients experienced ≥1 SAE. The most commonly reported TEAE was within the SOC infections and infestations (Upper respiratory tract infections, Bronchitis and Urinary tract infections); this could be expected knowing the mechanism of action of efgartigimod alfa. Other common TEAEs were (treatment related) headache, arthralgia, diarrhoea and abdominal pain. Few patients reported lymphocyte count decreased, however, the available data supports that there is no relation between 'Lymphocyte count decreased' and infection. During Trial ARGX-113-1705, a total of 7 patients all treated with efgartigimod alfa developed 10 events of neoplasm malignant.

While the mechanism of action does not indicate an effect on cardiac function, more patients treated with efgartigimod experienced an increase in QTcF. This difference has been explained by the higher third quartile (Q3; 75th percentile) value in the placebo-efgartigimod cohort and reassuringly, there is no excess in cardiovascular events. Overall, also the placebo-treated population had a high frequency of TEAEs which may reflect symptoms of the disease. Thus, the majority of TEAEs were reported with a comparable frequency between the efgartigimod alfa and the placebo group and besides of the adverse events mentioned above, the safety profile of efgartigimod alfa is considered to be acceptable. Nevertheless, infections (in particular mycotic and herpes viral infections), cardiac disorders, neoplasms and renal and urinary disorders) were more frequent in efgartigimod-treated patients. These risks are appropriately managed by warnings in the SmPC.

3.7.2. Balance of benefits and risks

The pivotal study was primarily aimed to evaluate the short-term effect of efgartigimod (after the first cycle) on seropositive gMG patients. Available data supports the efficacy of efgartigimod alfa in this population. No differences versus placebo were detected in seronegative patients (due to very high placebo response), who showed higher burden of the disease than seropositive patients. According to the efgartigimod alfa mechanism of action a differential response between both populations is not anticipated. However, due to no evidence to support a positive B/R on AChR-Ab seronegative patients, the indication is limited to AChR-Ab seropositive patients. The effect of efgartigimod as monotherapy has not been investigated and it is reflected in the labelling of the product as "add on" to standard therapy.

Taking into due consideration the limitations of the safety database, particularly in the long-term, it is considered that the safety profile of efgartigimod alfa in patients with gMG is acceptable. 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 is associated with a higher risk of infections, in particular, herpes viral infections and fungal infections. Although available data do not

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. However, these risks are appropriately managed by warnings in the SmPC and will be followed up in a PASS.

3.8. Conclusions

The overall benefit/risk balance of Vyvgart is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

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 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 granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that efgartigimod alfa is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendices

5.1. CHMP AR on similarity dated 23 June 2022

5.2. CHMP AR on New Active Substance (NAS) dated 23 June 2022