CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761304Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761304
Priority or standard	Priority voucher redemption
Submit date(s)	9/20/2022
Received date(s)	9/20/2022
PDUFA goal date	6/20/2023
Division/office	Division of Neurology I (DNI)
Review completion date	6/20/2023
Established/proper name	efgartigimod alfa and hyaluronidase-qvfc
(Proposed) proprietary name	Vyvgart Hytrulo
Pharmacologic class	combination of efgartigimod alfa, a neonatal Fc receptor blocker, and hyaluronidase, an endoglycosidase
Other product name(s)	Efgartigimod is also referred to as ARGX-113; hyaluronidase is also referred to as recombinant human hyaluronidase PH20 or rHuPH20
Applicant	argenx BV
Dosage form(s)/formulation(s)	Injection: 1,008 mg efgartigimod alfa and 11,200 Units hyaluronidase per 5.6 mL (180 mg/2,000 Units per mL) in a single-dose vial.
Dosing regimen	1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered subcutaneously in cycles of once weekly injections for 4 weeks. Administer subsequent treatment cycles based on clinical evaluation; the safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.
Applicant-proposed indication(s)/ population(s)	Generalized myasthenia gravis (gMG) in adult subjects
SNOMED CT code for proposed indication disease term(s)[1]	91637004 Myasthenia Gravis
Regulatory action	Approval
Approved dosage (if applicable)	1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered subcutaneously in cycles of once weekly injections for 4 weeks
Approved indication(s)/ population(s) (if applicable)	For the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive
SNOMED CT code for approved indication disease term(s)[1]	91637004 Myasthenia Gravis

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AChR-Ab	anti-acetylcholine receptor antibody
ADA	antidrug antibodies
AE	adverse event
AR	adverse reaction
AUC	area under the concentration-time curve
AUEC	area under the effect curve
BLA	biologics license application
CI	confidence interval
C_{max}	maximum plasma concentration
C_{trough}	concentration observed predose
ECG	electrocardiogram
EFG	efgartigimod
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
gMG	generalized myasthenia gravis
IgG	immunoglobulin gamma
IND	investigational new drug
ITT	intent-to-treat
MG-ADL	Myasthenia Gravis Activities of Daily Living
mITT	modified intent-to-treat
NDA	new drug application
NOAEL	no observed adverse effect level
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PT	preferred term
QMG	Quantitative Myasthenia Gravis
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
TEAE	treatment-emergent adverse event
TK	toxicokinetic

I. Executive Summary

1. Summary of Regulatory Action

Argenx BV submitted a biologics license application (BLA) 761304 for subcutaneously administered efgartigimod. Efgartigimod, a neonatal Fc receptor blocker was first approved in December 2021 as an intravenous administration for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

BLA 761304 was reviewed by a multidisciplinary review team that did not identify any issues that preclude approval. Each discipline has recommended approval. I, the signatory authority for this application, concur with those recommendations and agree that the benefit-risk assessment supports approval.

The Applicant submitted the results from Study 2001, an open-label study, that demonstrated comparative reductions in pathogenic AChR antibodies between the approved intravenous (IV) formulation of efgartigimod and the subcutaneous (SC) formulation. The results of that study provide substantial evidence of effectiveness for efgartigimod for the treatment of adults with gMG who are seropositive for the AChR antibody.

The Applicant requested a broad indication for the treatment of gMG without regard to antibody status. However, this application relies on the efficacy of the intravenous formulation of efgartigimod, which is approved for the AChR positive population only. Thus, the product will also be indicated in the AChR antibody positive population.

The available safety data show that the risks of efgartigimod are acceptable for its intended use. I concur that the identified risks can be mitigated through labeling and further evaluated during routine and enhanced pharmacovigilance as was requested for efgartigimod IV (i.e., serious events related to malignancy, reactivation of hepatitis B or latent tuberculosis, and infection including opportunistic infection). The overall benefit-risk is favorable as described in the Benefit-Risk framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document and product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease. Antibodies block the receptors for acetylcholine at the neuromuscular junction (NMJ), which prevents the muscle from contracting. It causes weakness in the skeletal muscles that worsens after periods of activity and improves after periods of rest. Symptoms may include ptosis, diplopia, facial weakness, difficulty swallowing, dyspnea, dysarthria, and weakness in the arms, hands, fingers, legs, and neck. Life-threatening respiratory failure (myasthenic crisis) occurs in 15 to 20% of patients and requires immediate emergency medical care. • MG most commonly affects young adult women (under 40) and older men (over 60), but it can occur at any age. MG is a rare disorder, with an estimated prevalence of 70 to 163 per million for acetylcholine receptor (AChR) MG, and around 1.9 to 2.9 per million for muscle specific kinase (MuSK) MG (Koneczny and Herbst 2019). Women are more often affected than men, with a female to male ratio of 3:1 for AChR-MG and a ratio of 9:1 for MuSK MG. • MG diagnosis can be supported by blood tests for known causative autoantibodies (AChR, MuSK, low-density lipoprotein receptor-related protein 4 [LRP4]), repetitive nerve stimulation, and single fiber electromyography. Eighty to 90% of patients with MG have autoantibodies against AChR (Nicolle 2016). MG with MuSK antibodies accounts for 1 to 10% of cases, while LRP4 antibodies are present in 1 to 3% of all patients with MG (Gilhus 2016).	MG is a serious, life-threatening disease that can cause disability due to weakness and death due to respiratory failure. Different autoantibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Available treatments include anticholinesterase medications such as mestinon or pyridostigmine; immunosuppressive drugs such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and rituximab; plasmapheresis and intravenous immunoglobulin; and thymectomy. Eculizumab (Soliris) and ravulizumab (Ultomiris) are C5 inhibitors that are FDA-approved for AChR antibody positive generalized myasthenia gravis. Both products carry a black box warning/REMS for serious meningococcal infections. Eculizumab and ravulizumab reduce complement-mediated destruction of the NMJ in patients with generalized MG (gMG) who are AChR antibody positive, but are not indicated for patients who are MUSK antibody positive or patients who are LRP4 antibody positive. • Efgartigimod (Vyvgart) is an intravenously administered neonatal Fc receptor blocker that is FDA-approved for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Treatment with efgartigimod leads to a reduction of circulating IgG antibodies.	Despite current treatment options, the severe weakness of myasthenia gravis may cause life-threatening respiratory failure (myasthenic crisis) in 15 to 20% of patients, which requires immediate emergency medical care. There remains a significant unmet clinical need for effective treatments for MG because not all patients with MG are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. The intravenous route of administration of the currently approved efgartigimod (Vyvgart) can be burdensome to patients.
Benefit	• The efficacy of intravenously injected efgartigimod (Vyvgart) was previously demonstrated in a double-blind placebo-controlled multicenter study that led to its initial approval in 2021 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. • Hyaluronidase (Hylenex, also referred to as rHuPH20 or PH20) was initially approved in 2005 as a tissue permeability modifier indicated as an adjuvant to increase the dispersion and absorption of other injected drugs. Hyaluronidase is not detected in the plasma after SC administration. • Efgartigimod with rHuPH20 is a fixed-combination product because both efgartigimod and hyaluronidase are considered active components. The contribution of	Study 2001, a randomized, open-label, parallel-group, multicenter study comparing the PD profile of efgartigimod PH20 SC and efgartigimod IV provided reliable and statistically persuasive evidence that efgartigimod PH20 SC was comparable to efgartigimod IV in AChR antibody level reduction over the dosing interval. This study was an open-label study and the secondary endpoint results were reported descriptively. Hence, the reported percentages of MG-ADL and QMG responders were not considered in support of the approval of this product; however, they were consistent with the previous results of the pivotal efficacy study that led to the approval of efgartigimod IV (Vyvgart) in 2021.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hyaluronidase is to facilitate absorption of the primary active component, efgartigimod. • Comparable reduction in AChR-Ab is considered an appropriate metric for bridging based on clear understanding on (1) the role of AChR-Ab in the disease pathophysiology in gMG; (2) the mechanism of action of efgartigimod; and (3) the clinical and PK/PD data from the efgartigimod IV development program. • For the current application, despite the difference in the shape of the PK profile, bridging for efficacy based on comparable AChR-Ab profiles between efgartigimod IV and a subcutaneously administered formulation of efgartigimod co-formulated with recombinant human hyaluronidase (referred to as efgartigimod PH20 SC), was demonstrated based on results from Study 2001, a randomized, open-label, parallel-group, multicenter study that enrolled 110 individuals with gMG. Subjects were randomized 1:1 to 4-weekly administrations of either efgartigimod IV 10 mg/kg or efgartigimod PH20 SC 1008 mg, with a 7-week follow-up period. PD comparability was evaluated at day 29 (i.e., 7 days after the fourth IV or SC administration). • AChR-Ab reduction was utilized as the primary basis for approval despite the fact that the primary endpoint in the protocol was the percent reduction from baseline in total IgG levels at day 29. • Safety of the efgartigimod PH20 SC was established based on the following: 1) the extent of exposure (AUC) of efgartigimod is comparable for the IV and the SC product and Cmax of the efgartigimod PH20 SC is lower than that for the IV product. Further, submitted long-term safety data after multiple dose administration of efgartigimod PH20 SC was found to be adequate.	
Risk and risk management	• The safety database included 168 subjects who received at least one dose of efgartigimod PH20 SC 1008 mg in Study 2001 and the open-label extension Study 2002. Subjects in Study 2002 received a median of 12.0 (min, max: 1, 24)	The safety database is adequate in terms of size and dosing given that generalized myasthenia gravis is a rare disease. Prescribing information should include language to alert the prescriber to the risk of injection site reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	doses of efgartigimod PH20 SC with a mean treatment duration of 161 days. Safety Concerns • There were no deaths in Study 2001. There was one death due to metastatic renal cell cancer in Study 2002 that was likely related to the subject's past history of renal cell cancer. • The most common TEAEs in subjects receiving efgartigimod PH20 SC in Study 2001 (occurring in at least 3 subjects) were injection site rash, injection site erythema, injection site pruritus, myasthenia gravis, injection site bruising, and injection site pain. • There appears to be a similar risk of infections in the efgartigimod PH20 SC and efgartigimod 10 mg/kg IV groups (18% and 20%, respectively). • There were more hypersensitivity-related adverse events in the efgartigimod PH20 SC group (18%) than in the efgartigimod IV group (4%) in Study 2001. There were no cases of anaphylaxis in either group. • There were more injection (local administration) site reactions in subjects who received efgartigimod PH20 SC (38%) than in subjects who received efgartigimod IV (6%) in Study 2001. • Over 100 use related events occurred in the HF validation studies, including use errors with critical tasks, which could result in medication errors. Use-related errors occurred with dose administration despite proposed risk mitigation strategies, including a training program.	The product will be indicated for healthcare provider administration only. Warnings and Precautions should include the risks of infections and hypersensitivity reactions, as was also described for the previously approved product efgartigimod IV (Vyvgart). As was done for efgartigimod IV, enhanced pharmacovigilence will be requested for serious events related to malignancy, reactivation of hepatitis B or of latent tuberculosis, and infection including opportunistic infection.

Abbreviations: gMG, generalized myasthenia gravis; IV, intravenous; QMG, Quantitative Myasthenia Gravis; REMS, risk evaluation and mitigation strategy; SC, subcutaneous; TEAE, treatment-emergent adverse events.

2.2. Conclusions Regarding Benefit-Risk

Myasthenia gravis is a serious, life-threatening disease that can result in significant morbidity and even mortality. Although there are several treatments approved to treat patients with gMG, there remains a need for effective treatments because not all patients with MG are able to receive, tolerate, or adequately benefit from the currently available clinical treatments.

Efgartigimod (Vyvgart) is an intravenously administered neonatal Fc receptor blocker that is FDA-approved for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Efgartigimod leads to a reduction of circulating immunoglobulin gamma (IgG) antibodies.

The Applicant has developed a subcutaneously administered formulation of efgartigimod co-formulated with recombinant human hyaluronidase, an approved tissue permeability modifier, (referred to as efgartigimod PH20 SC). Study 2001 is a randomized, open-label, parallel-group, multicenter study of efgartigimod PH20 SC and efgartigimod IV. The study enrolled 110 subjects with gMG who were randomized 1:1 to 4-weekly administrations of either efgartigimod IV 10 mg/kg or efgartigimod PH20 SC 1008 mg, with a 7-week follow-up period. In Study 2001 the Applicant has demonstrated a comparable pharmacodynamic (PD) effect of efgartigimod PH20 SC to efgartigimod IV, based on the percent change from baseline in AChR-Ab levels at day 29. The percent change in AChR-Ab levels were comparable between the efgartigimod PH20 SC and efgartigimod IV treatments, with the 90% CI within the range of 80% to 125%. A comparable AChR-Ab profile was considered an acceptable metric to support the approval because of the clear understanding of the mechanism of action of efgartigimod and the established causal relationship between AChR-Ab levels and the clinical endpoint. These results have provided reliable and persuasive evidence for the PD comparability between the SC and IV treatments. Refer to section 6.3 for more details

Although this study was not designed to establish efficacy based on clinical efficacy endpoints, and the secondary endpoint results were reported descriptively, the observed reduction in AChR-Ab levels at week 4 and the percentages of MG-ADL and QMG responders are consistent with the previous results of the pivotal efficacy study that led to the approval of efgartigimod IV (Vyvgart) in 2021.

The safety database included 168 subjects who received at least one dose of efgartigimod PH20 SC 1008 mg in Study 2001 and the open-label extension Study 2002. Subjects in Study 2002 received a median of 12.0 doses (min, max: 1, 24) of efgartigimod PH20 SC with a mean treatment duration of 161 days.

There were no deaths in Study 2001. There was one death due to metastatic renal cell cancer in Study 2002 that was likely related to the subject's history of renal cell cancer. The most common treatment-emergent adverse events (TEAEs) in subjects receiving efgartigimod PH20 SC in Study 2001 (occurring in at least three subjects) were injection site rash, injection site erythema, injection site pruritus, myasthenia gravis, injection site bruising, and injection site pain.

There appears to be a similar risk of infections in the efgartigimod PH20 SC and efgartigimod 10 mg/kg IV groups (18% and 20%, respectively). There were more hypersensitivity-related adverse events in the efgartigimod PH20 SC group (18%) than in the efgartigimod IV group (4%) in Study 2001. There were no cases of anaphylaxis in either group. There were more

injection (local administration) site reactions in subjects who received efgartigimod PH20 SC (38%) than in subjects who received efgartigimod IV (6%) in Study 2001.

The safety database is adequate in terms of size and dosing given that generalized myasthenia gravis is a rare disease. Prescribing information should include language to alert the prescriber to the risk of injection site reactions. Because of use-related errors and other concerns, the product will be indicated for healthcare provider administration only. Warnings and Precautions should include the risks of infections and hypersensitivity reactions, as was also described for the previously approved product efgartigimod IV (Vyvgart). As was requested for efgartigimod IV, enhanced pharmacovigilance will be requested for serious events related to malignancy, reactivation of hepatitis B or of latent tuberculosis, and infection including opportunistic infection.

II. Interdisciplinary Assessment

3. Introduction

Efgartigimod (Vyvgart) is an intravenously administered neonatal Fc receptor blocker that is Food and Drug Administration (FDA)-approved for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. The Applicant has developed a subcutaneously administered formulation of efgartigimod co-formulated with recombinant human hyaluronidase, an approved tissue permeability modifier, (referred to as efgartigimod PH20 SC).

The Applicant's proposed indication for efgartigimod PH20 subcutaneous (SC) is generalized myasthenia gravis (gMG) in adult subjects. This proposed indication differs from the indication of the approved product Vyvgart in that the limitation to patients who are anti-acetylcholine receptor (AChR) antibody positive has been removed by the Applicant. This issue is discussed in Section 6.3.2.

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease. Antibodies block the receptors for acetylcholine at the neuromuscular junction, which prevents the muscle from contracting. Patients with MG develop weakness in the skeletal muscles that worsens after periods of activity and improves after periods of rest. Symptoms may include ptosis, diplopia, facial weakness, difficulty swallowing, dyspnea, dysarthria, and weakness in the arms, hands, fingers, legs, and neck. Life-threatening respiratory failure (myasthenic crisis) occurs in 15 to 20% of patients and requires immediate emergency medical care. The diagnosis of MG can be supported by blood tests for known causative autoantibodies (AChR, MuSK, low-density lipoprotein receptor-related protein 4 [LRP4]), repetitive nerve stimulation, and single fiber electromyography. Eighty to 90% of patients with MG have autoantibodies against AChR (Nicolle 2016). MG with MuSK antibodies accounts for 1 to 10% of cases, while LRP4 antibodies are present in 1 to 3% of all patients with MG (Gilhus 2016).

U.S. Food and Drug Administration (FDA)-approved treatments include anticholinesterase medications, such as pyridostigmine bromide, eculizumab, ravulizumab, and efgartigimod administered intravenously. Immunosuppressive drugs such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and rituximab are used off-label for treatment. Some patients are treated with plasmapheresis, intravenous immunoglobulin, and/or thymectomy. Eculizumab (Soliris) and ravulizumab are C5 inhibitors that are FDA-approved for generalized myasthenia gravis, although both products carry a boxed warning/REMS for serious meningococcal infections. Eculizumab and ravulizumab reduce complement-mediated destruction of the NMJ in patients with generalized MG (gMG) who are AChR antibody positive but are not indicated for MuSK antibody positive or LRP4 antibody positive patients.

The efficacy of intravenously injected efgartigimod (Vyvgart) was previously demonstrated in a double-blind placebo-controlled multicenter study that led to its initial approval in 2021 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Hyaluronidase (Hylenex, also referred to as rHuPH20 or PH20) was initially approved in 2005 as a tissue permeability modifier indicated as an adjuvant to increase the dispersion and absorption of other injected drugs. In efgartigimod PH20 SC, coadministration with hyaluronidase allows for a larger volume to be injected subcutaneously. Hyaluronidase was not measurable in the systemic circulation at the clinically relevant dose of efgartigimod PH20 SC.

For the current application, the pharmacodynamic (PD) comparability to efgartigimod IV of efgartigimod PH20 SC was demonstrated by Study 2001, a randomized, open-label, parallel-group, multicenter study that enrolled 110 individuals with gMG. Subjects were randomized 1:1 to four weekly administrations of either efgartigimod intravenous (IV) 10 mg/kg or efgartigimod PH20 SC 1008 mg, with a seven-week follow-up period. PD comparability was evaluated at day 29 (i.e., 7 days after the fourth IV or SC administration).

Efgartigimod leads to a reduction of circulating immunoglobulin gamma (IgG) antibodies. The primary endpoint for this study was the percent reduction from baseline in total IgG levels at day 29. (b) (4) . The Agency recommended that the Applicant structure their arguments based on the pathogenic anti-AChR antibody, which forms the focus of the PD comparability review.

Note: The concentration of efgartigimod SC is 180 mg/mL. Investigators were instructed to administer 5.6 mL to subjects in the study which resulted in a dose of 1008 mg of efgartigimod being administered to subjects receiving the SC formulation.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

Because the pharmacokinetic (PK) profile of the SC and IV products differ substantially, a pharmacokinetic bridging approach between the IV and SC formulation is not applicable to establish the efficacy of the proposed efgartigimod PH20 SC product. Instead, pharmacodynamic comparability was established using serum anti-acetylcholine receptor antibody (AChR-Ab) as the bridging biomarker to support the approval of efgartigimod PH20 SC for the treatment of gMG. Three key efficacy review issues are listed as below and discussed further in Section 6.3.

3.1.1.1. Evaluation of Bridging Strategy Utilizing Acetylcholine Receptor-Antibody (AChR-Ab) Plasma Levels

3.1.1.2. Comparability of Reductions in AChR-Ab Between the IV and SC Formulations

3.1.1.3. (b) (4)

3.1.2. Key Safety Review Issues

The following list of key safety review issues is discussed Section 7.7.

3.1.2.1. Infections

3.1.2.2. Hypersensitivity

3.1.2.3. Injection Site Reactions

3.2. Approach to the Clinical Review

Safety was assessed by evaluating the results from the randomized, open-label, parallel-group study ARGX-113-2001 (referred to as Study 2001 in the text) and the supportive open-label extension study ARGX-113-2002 (Study 2002) in adults with generalized myasthenia gravis (91 seropositive for AChR-Ab and 20 seronegative in Study 2001). The safety assessment also included additional supportive safety data from subjects who transitioned from the open-label extension Study 1705 from the approved IV form of efgartigimod into Study 2002.

The effectiveness assessment focused on the adequacy of the pharmacodynamics-based bridging strategy in Study 2001 between the previously approved product efgartigimod IV and the new efgartigimod PH20 SC. The safety assessment was based on the Applicant's reports and data analyst and clinical reviewer analysis of the submitted data. Safety analyses were provided by FDA clinical data analyst Setareh Salimi Ashkezari, Ph.D.

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations[1] for Efgartigimod Alfa With Hyaluronidase

StudyIdentifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized2	Number of Centers and Countries
ARGX-113-2001	Adults with generalized myasthenia gravis	randomized, open-label, parallel-group	Drug: efgartigimod alfa with hyaluronidase SC (EFG PH20 SC) or efgartigimod alfa IV injection (EFG IV) Dosage: EFG IV 10 mg/kg or EFG PH20 SC 1008 mg once weekly for 3 weeks (4 administrations total) Number treated: 111 enrolled (1:1 ratio); 108 completed. EFG IV arm: 54; EFG PH20 SC arm: 54 Duration: 3 weeks treatment; 7 weeks follow-up	Primary: Percent reduction from baseline in total IgG levels at day 29 (i.e., 7 days after the fourth IV or SC administration) Secondary: Absolute values, change from baseline, and percent reduction from baseline in anti-acetylcholine receptor antibody (AChR-Ab) levels over time in AChR-Ab seropositive subjects	110 planned; 111 randomized	43 sites in 11 countries
ARGX-113-2002	Adults with generalized myasthenia gravis	Single-arm, open-label	Drug: EFG PH20 SC Dosage: EFG PH20 SC 1008 mg once weekly for 3 weeks (4 administrations total) per treatment period. Number treated: 178 Duration: 2 years; maximum of 14 treatment periods with >=28 days between treatment periods	Primary: Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAE) and adverse events of special interest (AESI); labs, physical exams, vital signs, ECG Secondary: MG-ADL score change from baseline; Percent reduction in AChR-Ab from baseline	201 planned; 178 enrolled	47 sites in 12 countries

StudyIdentifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized2	Number of Centers and Countries
ARGX-113-1705	Adults with generalized myasthenia gravis	single-arm, open-label	Drug: EFG IV Dosage: 10 mg/kg, infused over 1 hour in treatment periods of 1 infusion every 7 days for 3 weeks. Number treated: 145 Duration: ≤3 years	Primary: MG-ADL and QMG score change from baseline; Secondary: Levels of total IgG and subtypes, AChR-Ab levels, and MuSK-Ab. Incidence and severity of treatment-emergent AEs (TEAEs), SAEs, vital signs, electrocardiogram (ECG), and safety laboratory assessments	167 planned; 151 enrolled	44 sites in 14 countries
ARGX-113-1901	Healthy adult male subjects	Randomized, open-label, parallel-group	Drug: Efgartigimod SC + PH20 Dosage: Subjects randomized1:1:1:1 to the following:− Treatment A: single SC injection (comixed) of efgartigimod 750 mg + rHuPH20 2000 U/mL− Treatment B: single SC injection (comixed) of efgartigimod 1250 mg + rHuPH20 2000 U/mL− Treatment C: single SC injection (comixed) of efgartigimod 1750 mg + rHuPH20 2000 U/mL− Treatment D: single SC injection (comixed) of efgartigimod 10 mg/kg + rHuPH20 2000 U/mL Number treated: A: 8; B: 9; C: 8; D: 8 Duration: 1 day	Primary: Total IgG and IgG subtype (IgG1, IgG2, IgG3, and IgG4) concentrations and derived absolute change and percent change from baseline. Secondary: serum PK parameters: C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}72h}$, $AUC_{0\text{-}96h}$, $AUC_{0\text{-}336h}$, $AUC_{0\text{-}inf}$, $\%AUC_{extra}$, λz, $t_{1/2}$, CL/F, and Vz/F. Incidence and severity of treatment-emergent AEs (TEAEs), SAEs, vital signs, electrocardiogram (ECG), and safety laboratory assessments	33 enrolled; 33 completed;	1

StudyIdentifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized2	Number of Centers and Countries
ARGX-113-1907	Healthy adult male and female subjects	Randomized, open-label, parallel-group	Drug: Efgartigimod IV and efgartigimod PH20 SC Dosage: Once weekly Efgartigimod IV 10 mg/kg; Efgartigimod PH20 SC 1008 mg Number treated: 27 IV, 27 SC Duration: 3 weeks	Primary: Percentage reduction in total IgG levels, compared to baseline, at day 29 (week 4), 7 days after the fourth IV or SC administration of efgartigimod Secondary: Serum levels of efgartigimod and derived PK parameters; Incidence and severity of treatment-emergent AEs (TEAEs), SAEs, vital signs, ECG, and safety laboratory assessments	54 enrolled, 50 subjects completed	1

Source: Reviewer.
1 Includes all submitted clinical trials, even if not reviewed in-depth.
2 If no randomization, then replace with "Actual Enrolled."
Abbreviations: AE, adverse event; AESI, adverse event of special interest; BID, twice daily; DB, double-blind; ECG, electrocardiogram; EFG, efgartigimod; IgG, immunoglobulin gamma; LTE, long-term extension; MC, multicenter; MG-ADL, Myasthenia Gravis Activities of Daily Living; N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; PK, pharmacokinetics; R, randomized; SAEs, serious adverse events; SC, subcutaneous; TEAE, treatment-emergent adverse event; T_{max}, time to maximum concentration; h, hour; d, day; wk, week(s); mo, month(s); y, y

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2.1.1, 6.2.1.4
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6.2.1.1, 6.2.1.4
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Not applicable.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Efgartigimod is a human IgG1 antibody fragment and an Fc receptor (FcRn) blocker.
Mechanism of action	Efgartigimod is a human IgG1 antibody fragment engineered to bind with neonatal FcRn, resulting in the reduction of circulating IgG, including autoantibodies.
Active moieties	Efgartigimod
QT prolongation	Dedicated QTc prolongation study was not conducted. Efgartigimod is a human IgG1 antibody fragment with a MW of 54 kD, and no direct ion channel effects are expected.
	General Information
Bioanalysis	The serum concentrations of efgartigimod in studies ARGX-113-1901 and ARGX-113-1907 were determined by validated enzyme-linked immunosorbent assay (ELISA) method. A sandwich immunoassay on the Gyrolab Bioaffy system was used for the determination of efgartigimod in serum samples from ARGX-113-2001 and ARGX-113-2002. The methods were adequate for quantification of serum efgartigimod concentrations. The serum AChR-Ab level in Study 2001 was quantified using a commercialized kit with a radioimmunoassay (RIA) method which was validated and adequate to support the bridging using AChR-Ab.
Healthy subjects versus subjects	Clinically relevant differences in PK are not expected between healthy subjects and subjects
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Following the fourth weekly dose of efgartigimod PH20 SC 1008 mg, mean (SD) values for C_{max}, C_{trough}, and $AUC_{0\text{-}168h}$ were reported to be 50.1 (21.2) µg/mL, 19.8 (6.09) µg/mL, and 5841 ± 1506 µg·h/mL, respectively, from Study ARGX-113-1907 (Study 1907).
Range of effective dose(s) or exposure	Only a single dose-level, efgartigimod PH20 SC 1008 mg administered weekly for a total of four infusions per treatment cycle was studied in subjects with gMG (Study ARGX-113-2001 [Study 2001] and the open-label extension Study ARGX-113-2002 [Study 2002]).
Maximally tolerated dose or exposure	The highest dose of efgartigimod PH20 SC evaluated in humans was a single dose of 1750 mg in healthy subjects (n=8) in Study 1901.
Dose proportionality	Efgartigimod exposures (C_{max} and AUC_{inf}) were approximately dose-proportional at the dose range of 750 to 1750 mg efgartigimod PH20 SC (up to 1.75 times the recommended dosage, Study ARGX-113-1901).
Accumulation	Following four weekly doses of efgartigimod PH20 SC 1008 mg within a treatment cycle, the accumulation is expected to be minimal.
Time to achieve steady-state	Steady-state exposures of efgartigimod are expected to be achieved within end of the treatment cycle (Q1W*4).

Characteristic	Drug Information
Bridge between to-be-marketed and clinical study formulations	The to-be-marketed formulation was used in Study ARGX-113-2001 and the open-label extension Study ARGX-113-2002.
	Absorption
Bioavailability	The absolute bioavailability after a single dose of efgartigimod SC 10 mg/kg (without rHuPH20) was 47.21% (90% confidence interval [CI]: 34.36%, 64.86%). Efgartigimod $AUC_{0\text{-}inf}$ (mean [SD]) were slightly higher when efgartigimod SC 10 mg/kg was administered with 2000 U/mL rHuPH20 (3632 [1185] µg.h/mL) compared with efgartigimod SC without rHuPH20 (3260 [1470] µg.h/mL).
T_{max}	Median (Min-Max) was 48 (8-96) hours following 4-weekly administrations of efgartigimod PH20 SC 1008 mg
Food effect (fed/fasted) Geometric least square mean and 90% CI	Efgartigimod is administered subcutaneously, and therefore food-effect is not relevant.
	Distribution
Volume of distribution	Based on population PK analyses, the mean estimate of volume of distribution was 15-20 L.
Plasma protein binding	Plasma protein binding was not determined.
Drug as substrate of transporters	Efgartigimod is a human IgG1 antibody fragment and is unlikely to be affected by drug transporters; therefore, no transporter-mediated drug-interaction studies were conducted.
	Elimination
Mass balance results	No dedicated mass balance study was conducted. In Study 1501 part I, <0.1% of the dose was excreted unchanged in urine in the dose range of 10 mg/kg to 50 mg/kg in healthy subjects (n=4 per dose group).
Clearance	Based on population PK analyses, the mean estimate of clearance was 0.108 L/h.
Half-life	Mean terminal half-life was 80-120 hours (3 to 5 days).
Metabolic pathway(s)	Efgartigimod is a human IgG1 antibody fragment and is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids.
	Intrinsic Factors and Specific Populations
Body weight	Comparable AChR-Ab reduction between efgartigimod IV 10 mg/kg and efgartigimod PH20 SC 1008 mg administrations was observed in Study 2001 across body weights, supporting the fixed dose of efgartigimod PH20 SC 1008 mg.
Age	No age-based dose adjustments are needed.
Renal impairment	No dose adjustment is needed for patients with mild renal impairment. There are insufficient data to evaluate the impact of moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) and severe renal impairment (eGFR <30 mL/min/1.73 m^2) on pharmacokinetic parameters of efgartigimod.
Hepatic impairment	No dose adjustment is needed in patients with hepatic impairment.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Efgartigimod is neither subject to CYP450 enzymes nor expected to interfere with cytokine levels. Therefore, no CYP450-mediated drug-interaction studies were conducted.
Inhibition/induction of transporter systems	Efgartigimod is a human IgG1 antibody fragment and is unlikely to be affected by drug transporters; therefore, no transporter-mediated drug-interaction studies were conducted.
Interaction with other therapeutic moieties	Closely monitor for reduced effectiveness of moieties that bind to the human FcRn (i.e., immunoglobulin products, monoclonal antibodies, or antibody derivates containing the human Fc domain of the IgG subclass), when concomitant use is necessary. When long-term use of such medications is essential for patient care, stop efgartigimod use and consider alternative gMG medications.
Impact on immunizations	Vaccination with live-attenuated or live vaccines is not recommended during treatment with efgartigimod. Administer all age-appropriate vaccines according to immunization guidelines before initiation of treatment with efgartigimod.
	Immunogenicity (if Applicable)
Bioanalysis	Immunogenicity assessments were conducted using affinity capture elution (ACE) bridging ELISA assay to determine the exposures of antidrug antibodies (ADA).
Incidence	In Study 2001, following up to 10 weeks of weekly treatment with efgartigimod PH20 SC 1008 mg, 35% (19/55) of subjects developed antibodies to efgartigimod, and 4% (2/55) of subjects developed neutralizing antibodies to efgartigimod.
Clinical impact	Based on the limited number of subjects who tested positive for ADA and neutralizing antibodies, the available data are too limited to make definitive conclusions regarding an effect on pharmacokinetics, safety, or efficacy of efgartigimod.

Source: Applicant's summary of clinical pharmacology studies, and Integrated Review of BLA 761195 Section 5
Abbreviations: ACE, affinity capture elution; AChR-Ab, anti-acetylcholine receptor antibody; ADA, antidrug antibodies; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate; gMG, generalized myasthenia gravis; OL, open-label; PK, pharmacokinetic; SC, subcutaneous; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

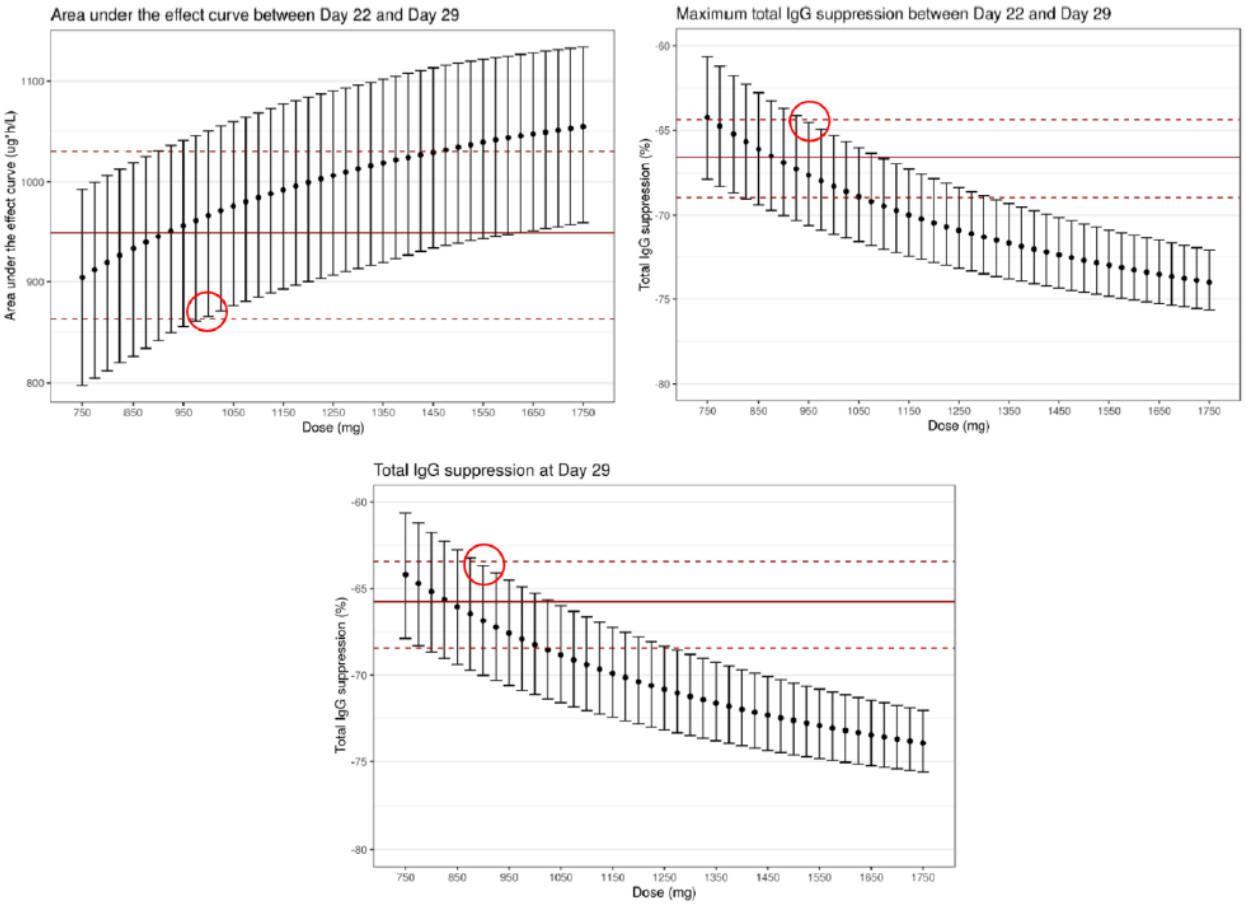
6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Dose Selection Rationale

To select the dose of efgartigimod PH20 SC for the Phase 3 Study 2001, a population PK/PD approach was taken using the data of Study ARGX-113-1901, to target a similar PD effect as achieved with the efgartigimod IV 10 mg/kg dose which was demonstrated to be safe and efficacious. Based on the PK/PD model, the Applicant performed simulations for a typical subject weighing 70 kg for a dose range of 750 to 1750 mg. For the three metrics including area under the effect curve (AUEC) day 22 to 29, maximal IgG reduction between day 22 and 29, and IgG reduction at day 29, the efgartigimod PH20 SC doses that provided comparable median values to efgartigimod IV 10 mg/kg were 925 mg, 900 mg, and 825 mg, respectively (Figure 1).

To maximize the probability of clinical improvement, both the median values and the 90% confidence interval (CI) ranges of the PD outcome parameters were considered in the dose selection. An efgartigimod PH20 SC dose was selected based on the predicted median value of the three metrics reaching at least the median value of the 10 mg/kg IV dosing and the lower limits of the 90% CI falling within the lower limits of the IgG reduction. As shown in Figure 1, 1008 mg was the dose which met all these conditions. The effect of body weight on efgartigimod exposure is limited and not clinically relevant (refer to Section 6.1.2), which further justified a fixed dose of efgartigimod PH20 SC 1008 mg.

Figure 1. Simulations of Total IgG Reduction: AUEC Day 22 to 29, Maximal IgG Reduction Between Day 22 and 29, and IgG Reduction at Day 29 After Weekly Doses of 750 to 1750 mg Efgartigimod PH20 SC



Source: Applicant's summary of clinical pharmacology studies, page 43, Figure 14. Solid and dashed red lines represent median and 5th and 95th percentile values obtained with 10 mg/kg IV q7d efgartigimod. Black points and bars represent median and 5th and 95th percentile values obtained with q7d doses of efgartigimod PH20 SC. Red circles indicate the SC dose for which the lower limit of its confidence interval on these outcome parameters coincides with that of the IV dose.
Abbreviations: IgG, immunoglobulin gamma; SC, subcutaneous

Efgartigimod was co-formulated with 2000 U/mL of rHuPH20. This enzyme is a permeation enhancer, allowing for a larger volume to be injected SC. At a concentration of 180 mg/mL for efgartigimod and 2000 U/mL for rHuPH20, 5.6 mL of solution delivers 1008 mg of efgartigimod and 11,200 U of rHuPH20.

Several monoclonal antibodies co-formulated with rHuPH20 have been approved for SC administration, including rituximab (MabThera SC/ Rituxan Hycela), trastuzumab (Herceptin SC/Herceptin Hylecta), pertuzumab/trastuzumab (Phesgo), and daratumumab (Darzalex SC/Darzalex Faspro), with an rHuPH20 concentration of 2,000 U/mL for an injection volume in the range of 5 to 15 mL. The proposed efgartigimod PH20 SC drug product has the same rHuPH20 concentration (2000 U/mL) and a similar injection volume (5.6 mL) as the approved products.

Based on Study ARGX-113-2001 and Study ARGX-113-1907, the selected doses for efgartigimod and rHuPH20 in the SC formulation were appropriate, as the efgartigimod PH20 SC demonstrated comparable AChR-Ab reduction with the efgartigimod IV 10 mg/kg dose

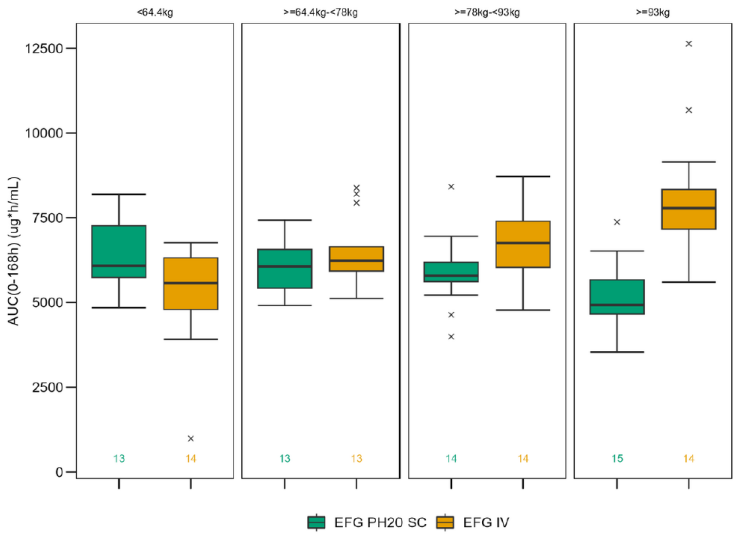
(Refer to Section 6.3.2). The recommended dosing regimen of efgartigimod PH20 SC is a treatment cycle comprising four weekly injections of efgartigimod PH20 SC 1008 mg over a (b) (4) week period, and the frequency of treatment cycles may vary by patient. The dosing frequency is consistent with recommended dosing of approved efgartigimod IV formulation. Please refer to Section 7 for additional evaluation on safety.

6.1.2. Justification of Fixed Dosing for Subjects With Different Body Weights

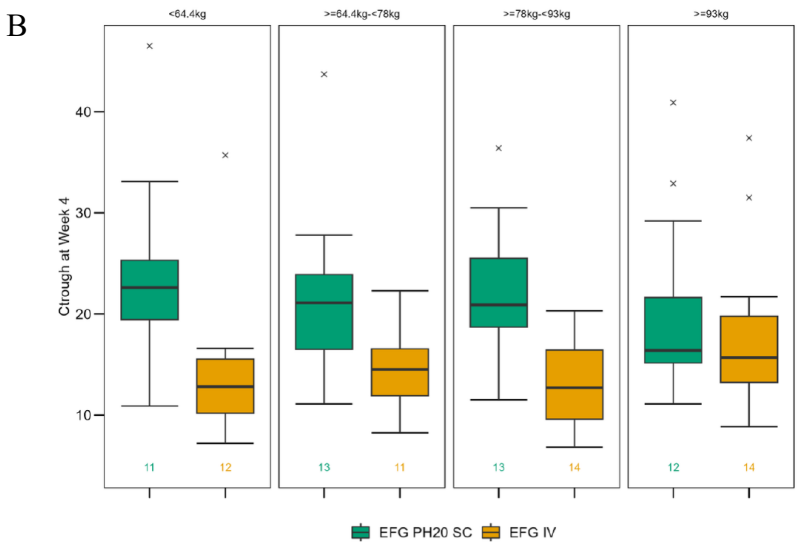
The PK exposures of efgartigimod were compared between efgartigimod PH20 SC 1008 mg and the efgartigimod IV 10 mg/kg treatments in Study ARGX-113-2001 (Figure 2). Following SC administration, there was a trend towards a decrease in efgartigimod C_{trough} and area under the concentration-time curve ($AUC_{0\text{-}168h}$) with increasing body weight, while an opposite trend was observed following IV administration (Figure 2). Although the $AUC_{0\text{-}168h}$ was lower following SC administration compared to IV administration at the highest body weight group, the C_{trough} from SC arm was not lower than the C_{trough} from the IV arm in any of the four body weight groups. The impact of the difference in PK exposure on PD effect was evaluated (Figure 3), which showed comparable AChR-Ab reduction between IV and SC administrations across body weights, supporting the fixed dose of efgartigimod PH20 SC 1008 mg.

Figure 2. Simulated $AUC_{0\text{-}168h}$ (A) and Observed C_{trough} at Day 29 (B) After the Fourth Weekly Administrations of Efgartigimod PH20 SC 1008 mg or Efgartigimod IV 10 mg/kg by Body Weight Quartiles in Study 2001

A

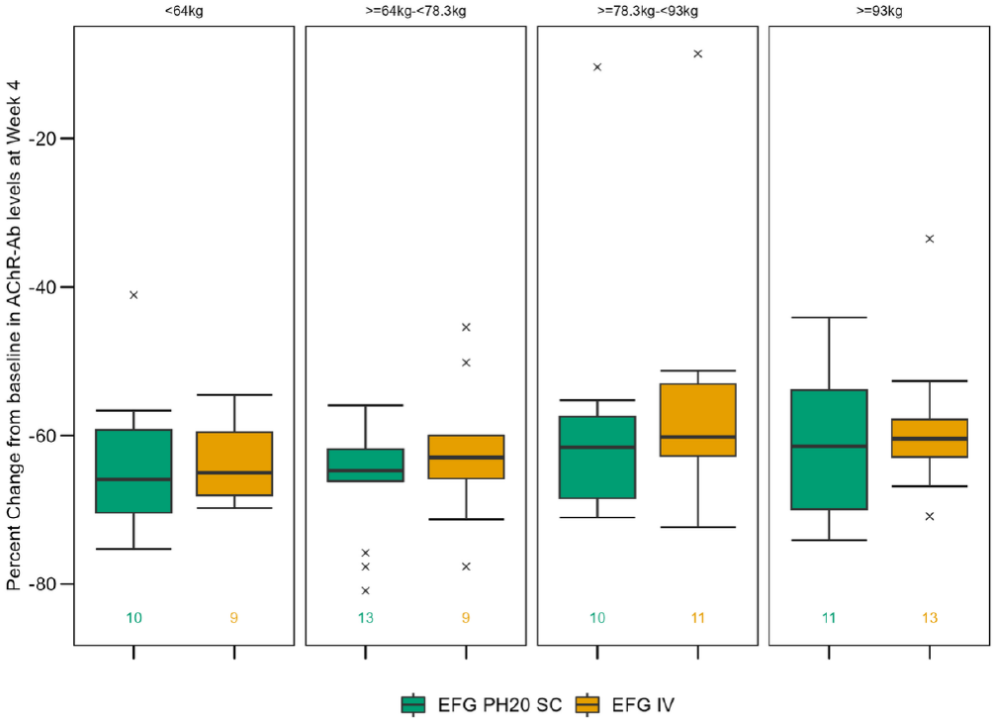


B



Source: Applicant's IR response submitted on May 26, 2023, page 3-4, Figure 1 and Figure 2. Note: The $AUC_{0\text{-}168h}$ (µg×h/mL) was predicted using pop-PK model and C_{trough} (µg/mL) was observed data in Study 2001. The box represents the range between lower and upper quartile. The solid line represents the median. Values present the number of observations.
Abbreviations: AUC, area under the concentration-time curve; EFG, efgartigimod; IV, intravenous;

Figure 3. AChR-Ab Percent Change From Baseline at Day 29 After 4-Weekly Administrations of Efgartigimod PH20 SC 1008 mg or Efgartigimod IV 10 mg/kg by Body Weight Quartiles in Study 2001



Source: Applicant's IR response submitted on May 26, 2023, page 6, Figure 3. Note: The box represents the range between lower and upper quartile. The solid line represents the median. Values present the number of observations.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; IV, intravenous

Besides the comparable PD effect, the projected difference in the PK exposure was not found to be significant across different body weights following SC treatment with the proposed dosing

regimen. Using a population PK model, the $AUC_{0\text{-}168h}$ after the fourth administration of efgartigimod PH20 SC 1008 mg was simulated for subjects with body weight 50.4 kg and 112.1 kg (the 5th and 95th percentile body weight in ARGX-113-2001 PH20 SC treatment group, respectively). Compared to a reference subject with body weight of 78.3 kg (median in ARGX-113-2001 PH20 SC treatment arm), a body weight of 50.4 kg was associated with a relative difference in $AUC_{0\text{-}168h}$ of +22.5% (90% CI: +15.8%, +29.5%), and a body weight of 112 kg was associated with a relative $AUC_{0\text{-}168h}$ reduction of -15.4% (90% CI: -20.4%, -10.1%). Overall, the estimated ratios of $AUC_{0\text{-}168h}$ were within 80% - 125%, suggesting a limited effect of body weight on the exposure of efgartigimod following the fixed SC dosing in the body weight range of 50.4 kg to 112.1 kg.

Of note, the recommended dose of Vyvgart (efgartigimod for IV use) in patients weighing 120 kg or more is 1200 mg per infusion. Hence, further increase of body weight beyond 120 kg is not expected to result in a larger difference in $AUC_{0\text{-}168h}$ between IV and SC treatments.

In summary, the influence of body weight on efgartigimod exposure following fixed dosing of efgartigimod PH20 SC 1008 mg was limited and did not result in a significant difference in AChR-Ab reduction between IV and SC treatments across body weights. Therefore, a fixed dose of efgartigimod PH20 SC 1008 mg is justified for all body weights.

6.2. Clinical Studies Intended to Demonstrate Efficacy

6.2.1. Study ARGX-113-2001

6.2.1.1. Design, Study ARGX-113-2001

Study 2001 was a Phase 3, randomized, open-label, parallel-group study to compare the pharmacodynamics, pharmacokinetics, efficacy, safety, tolerability, and immunogenicity of multiple subcutaneous injections of efgartigimod PH20 SC to multiple intravenous infusions of efgartigimod IV in subjects with generalized myasthenia gravis.

The primary objective was to demonstrate that the pharmacodynamic (PD) effect of injections of 1008 mg efgartigimod PH20 SC, administered once weekly for four administrations, is noninferior to that of IV infusions of efgartigimod at a dose of 10 mg/kg administered once weekly for four administrations.

The secondary objectives are listed below.

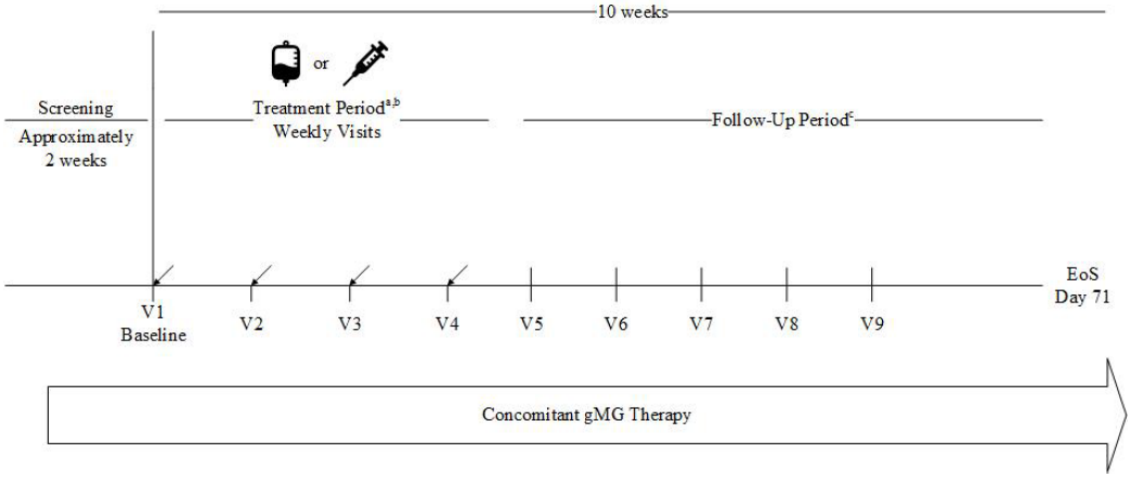
- To compare the PD effect of efgartigimod PH20 SC and efgartigimod IV over time
- To evaluate the pharmacokinetics (PK) of efgartigimod PH20 SC and efgartigimod IV
- To evaluate the safety, tolerability, and immunogenicity of efgartigimod PH20 SC and efgartigimod IV
- To evaluate the clinical efficacy of efgartigimod PH20 SC and efgartigimod IV

Basic Study Design:

Study 2001 was a randomized, open-label, parallel-group, multicenter (43 sites), multinational (11 countries) study in subjects with gMG. Eligible subjects were AChR-Ab seropositive or seronegative. The planned study size was N=110; the actual number randomized in this study was N=111. There were 110 subjects in the safety analysis set and the intent-to-treat (ITT) and modified intent-to-treat (mITT) analysis sets (55 subjects in the efgartigimod PH20 SC arm and 55 subjects in the efgartigimod IV arm). Randomization was stratified by Japanese versus non-Japanese subjects. With non-Japanese subjects, randomization was further stratified by AChR-Ab status. There were 91 (82%) subjects who were seropositive for acetylcholine receptor (AChR) antibodies and 20 (18%) subjects who were seronegative for AChR antibodies. There were 45 and 46 AChR antibody-positive subjects in the efgartigimod PH20 SC and IV arms, respectively.

The total study duration was approximately 12 weeks (2 weeks screening, 3 weeks treatment, 7 weeks follow-up). Treatment was given once weekly starting at baseline on day 1. Efgartigimod IV 10 mg/kg was administered once weekly for four infusions. Efgartigimod PH20 SC 1008 mg was administered once weekly for four injections. The study design is shown in the following figure, copied from the submission.

Figure 4. Schema for Study ARGX-113-2001



Source: Study 2001 Protocol, figure 1
EoS = end of study; gMG = generalized myasthenia gravis; IMP = investigational medicinal product; IV = intravenous(ly); PH20 = rHuPH20 (recombinant human
PH20 hyaluronidase); SC = subcutaneous; V = visit
a subjects will be randomized in a 1:1 ratio to either the efgartigimod IV 10 mg/kg treatment arm or the efgartigimod PH20 SC 1008 mg treatment arm.
Subjects will receive IMP every 7 days for 4 administrations.
b Subjects receiving efgartigimod PH20 SC or their caregivers will be trained in self-administration of the IMP. Once a subject or caregiver is considered competent to self-administer, they will be allowed to self-administer the IMP on site under supervision of the site staff starting at V2.
c The follow-up period consists of weekly visits through V9, followed by a 2-week period between V9 and EoS.

Study 2001 Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for Study 2001 is the percent reduction from baseline in total IgG levels at day 29 (i.e., 7 days after the fourth IV or SC administration).

Secondary Efficacy Endpoints for Study 2001

- Absolute values, change from baseline, and percent reduction from baseline in total IgG levels over time
- Absolute values, change from baseline, and percent reduction from baseline in anti-acetylcholine receptor antibody (AChR-Ab) levels over time in AChR-Ab seropositive subjects
- Absolute values, change from baseline, and percent reduction from baseline in IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time
- AUEC of the percent reduction from baseline total IgG and similar AUEC for each IgG subtype per dosing interval (days 1-8, days 8-15, days 15-22, and days 22-29), days 1-29, and over the entire study (days 1-71)
- PK parameters: maximum concentration (C_{max}) (after all doses for the IV treatment arm) and concentration observed predose (C_{trough}) (after all doses for the IV and SC treatment arms)
- Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod
- Incidence and prevalence of antibodies against rHuPH20 in the SC treatment arm
- Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram (ECGs) results
- Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders
- Number and percentage of Quantitative Myasthenia Gravis (QMG) responders
- Change from baseline in MG-ADL total score over time
- Change from baseline in QMG score over time

The MG-ADL is a categorical patient-reported outcome scale that assesses the impact on daily function of eight signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 024). The MG-ADL scale is a suitable measure of efficacy for clinical studies in patients with myasthenia gravis. Note that the MG-ADL scale was also used in the clinical studies that led to the approval of eculizumab, ravulizumab, and efgartigimod for gMG.

Figure 5. Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Source: (Muppidi 2012)
Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living

The QMG, shown in the figure below, is a physician assessment scoring system that consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item) and respiratory (1 item). These 13 items are objectively and quantitatively assessed and each graded from 0 to 3, with 3 being the most severe, providing a total QMG score ranging from 0 to 39. The QMG score is adequate as a secondary endpoint.

Figure 6. Quantitative Myasthenia Gravis (QMG) Score

Quantitative MG score

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11–60	1–10	Spontaneous	____
Ptosis (upward gaze), seconds	61	11–60	1–10	Spontaneous	____
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	____
Swallowing 4 oz. water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing /choking or nasal regurgitation	Cannot swallow (test not attempted)	____
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	Dysarthria at 10–29	Dysarthria at 9	____
Right arm outstretched (90 degree sitting), seconds	240	90–239	10–89	0–9	____
Left arm outstretched (90 degree sitting), seconds	240	90–239	10–89	0–9	____
Vital capacity, % predicted	≥80	65–79	50–64	<50	____
Right-hand grip, kgW					
Men	≥45	15–44	5–14	0–4	____
Women	≥30	10–29	5–9	0–4	____
Left-hand grip, kgW					
Men	≥35	15–34	5–14	0–4	____
Women	≥25	10–24	5–9	0–4	____
Head lifted (45 degree supine), seconds	120	30–119	1–29	0	____
Right leg outstretched (45 degree supine), seconds	100	31–99	1–30	0	____
Left leg outstretched (45 degree supine), seconds	100	31–99	1–30	0	____
			Total QMG score (range, 0–39)		

Source: (Jaretzki et al. 2000)
Abbreviations: QMG, Quantitative Myasthenia Gravis

Reviewer's comment: (b) (4) [redacted]

6.2.1.2. Eligibility Criteria, Study ARGX-113-2001

The criteria listed below from the submitted protocol appear adequate to enroll subjects with gMG representative of the U.S. population.

Key Inclusion Criteria

- Adult subjects who were diagnosed with gMG with confirmed documentation and supported by at least one of the following:
  - History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation
  - History of positive edrophonium chloride test
  - Demonstrated improvement in MG signs upon treatment with oral acetylcholinesterase (AChE) inhibitors as assessed by the treating physician
- An MG-ADL total score of ≥5 points, with >50% of the total score attributed to nonocular symptoms, at screening and baseline
- Receiving a stable dose of concomitant therapy for gMG

6.2.1.3. Statistical Analysis Plan, Study ARGX-113-2001

The determination of the noninferiority (NI) of efgartigimod PH20 SC with efgartigimod IV is based on the total IgG percent reduction at day 29 utilizing a noninferiority margin of 10.

The hypotheses for the evaluation of noninferiority are as follows:

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

Reviewer's comment: The Applicant proposed using 10% as the NI margin for Study ARGX-113-2001. The acceptability of bridging was determined by the review team primarily based on comparability of PD effect between IV and SC treatment arms using the standard bioequivalence criteria (90% CI of geometric mean ratio (GMR) as compared to 80%-125%). Although the proposed 10% NI margin was not accepted as the main criteria during the review, the results suggested that the upper limit of the CI (2.41%) based on AChR-Ab reduction was below the protocol-specified NI margin of 10%, which supports that the efgartigimod PH20 SC was NI to efgartigimod IV. Please refer to Section 14.5 Pharmacometrics Assessment for additional details.

6.2.1.4. Results of Analyses, Study ARGX-113-2001

Demographics for the pivotal PD bridging Study 2001 are described in the following tables. Study 2001 enrolled 110 subjects. Sixty-five (59%) were female. This sex imbalance is consistent with the natural history of myasthenia gravis. At screening, age and race were adequately balanced between the efgartigimod-rHuPH20 SC and efgartigimod IV groups. Overall, there appears to be an acceptable balance of demographic characteristics between the efgartigimod-rHuPH20 SC and efgartigimod IV groups that adequately represents the demographics of the intended patient population.

Table 6. Baseline Demographic and Clinical Characteristics, Study ARGX-113-2001

	ARGX-113-2001	
Characteristic	**EFG SC N=55**	**EFG IV N=55**
Sex, n (%)		
Female	31 (56.4)	34 (61.8)
Male	24 (43.6)	21 (38.2)
Age, years		
Mean (SD)	50.9 (15.8)	55.8 (15.3)
Median (min, max)	53 (19, 84)	59 (24, 83)
Age group, years, n (%)		
≥65 years	12 (21.8)	18 (32.7)
18 to 64 years	43 (78.2)	37 (67.3)
Age group ≥75, years, n (%)		
≥75	2 (3.6)	5 (9.1)
Race, n (%)		
Asian	4 (7.3)	4 (7.3)
Multiple	1 (1.8)	0
White	50 (90.9)	51 (92.7)
Ethnicity, n (%)		
Hispanic or Latino	3 (5.5)	2 (3.6)
Not Hispanic or Latino	52 (94.5)	53 (96.4)
Country of participation, n (%)		
Georgia	9 (16.4)	11 (20.0)
Poland	18 (32.7)	18 (32.7)
United States	9 (16.4)	10 (18.2)
Others	19 (34.5)	16 (29.1)
Region of participation, n (%)		
Japan	4 (7.3)	4 (7.3)
Rest of World	42 (76.4)	41 (74.5)
United States	9 (16.4)	10 (18.2)
Is in United States, n (%)		
United States	9 (16.4)	10 (18.2)
Non-United States	46 (83.6)	45 (81.8)

Source: adsl.xpt; Software: R
Abbreviations: EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment group; n, number of subjects with given characteristic; SC, subcutaneous; SD, standard deviation

Table 7. Subject Screening and Enrollment, Studies ARGX-113-2001

Disposition	Study ARGX-113-2001
Subjects screened	153
Screening failures	42
Subjects enrolled	111
Subjects randomized	111
Subjects planned to roll over	NA
Subjects rolled over	NA
Subjects treated	110

Source: ds.xpt and Clinical Study Report; Software: R

Table 8. Subject Disposition, Trial ARGX-113-2001

	ARGX-113-2001		
Disposition Outcome	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)
Subjects randomized	55 (100)	56	NA
ITT population	55 (100)	55 (100)	0 (0, 0)
mITT population	55 (100)	55 (100)	0 (0, 0)
Per-protocol population	49 (89.1)	49 (89.1)	0 (0, 0)
Safety population	55 (100)	55 (100)	0 (0, 0)
Treatment received	55 (100)	55 (100)	0 (0, 0)
Completed	52 (94.5)	55 (100)	-5.5 (-11.5, 0.5)
Discontinued study drug	3 (5.5)	1 (1.8)	3.6 (-3.3, 10.6)
Adverse event	2 (3.6)	0	3.6 (-1.3, 8.6)
Lack of efficacy	0	0	0 (0, 0)
Other	1 (1.8)	0	1.8 (-1.7, 5.3)
Withdrawal by subject	0	1 (1.8)	-1.8 (-5.3, 1.7)

Source: ds.xpt and adsl.xpt; Software: R
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; EFG, efgartigimod; ITT, intent-to-treat; IV, intravenous; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group; NA, not applicable; SC, subcutaneous

One subject (Subject ID: [redacted] (b) (6)) was randomized to the EFG IV arm but did not receive efgartigimod due to an AE of pyrexia.

Efficacy Results – Primary Endpoint

The primary PD endpoint was the percent reduction from baseline in total IgG levels at day 29 (i.e., 7 days after the fourth IV or SC administration).

The following table, copied from the submission, shows the results of the Applicant's analysis of the primary endpoint. The least-squares mean estimate of the percent change from baseline in total IgG level at day 29 was −66.4% (95% CI: −68.91 to −63.86) in the efgartigimod PH20 SC arm and −62.2% (95% CI: −64.67 to −59.72) in the efgartigimod IV arm. The corresponding least-squares mean difference in the percent change from baseline in total IgG levels at day 29 between the 2 arms (efgartigimod PH20 SC versus efgartigimod IV) was −4.2% (95% CI: −7.73 to −0.66) in favor of efgartigimod PH20 SC. Therefore, the magnitude of the difference between the two groups was below the prespecified NI margin of 10% allowing for the conclusion that efgartigimod PH20 SC was noninferior to efgartigimod IV in total IgG level reduction at day 29.

Table 9. ANCOVA Analysis of Percent Change From Baseline in Total IgG Level at Day 29

	EFG PH20 SC			EFG IV			EFG PH20 SC vs EFG IV		
	N	LS mean	95% CI	N	LS mean	95% CI	LS mean difference	95% CI	p-value
mITT	50	−66.4	−68.91 to −63.86	52	−62.2	−64.67 to −59.72	−4.2	−7.73 to −0.66	<0.0001
PP	48	−66.5	−69.13 to −63.89	49	−61.8	−64.41 to −59.23	−4.7	−8.38 to −1.00	<0.0001
AChR-Ab seropositive participants in mITT	41	−66.9	−69.78 to −64.02	43	−62.4	−65.22 to −59.59	−4.5	−8.53 to −0.46	<0.0001

Source: Study 2001 CSR, table 30
Note: ANCOVA analysis included randomized treatment as a factor and baseline total IgG level as a covariate. There were 5 subjects in the efgartigimod PH20 SC arm and 3 subjects in the efgartigimod IV arm who were excluded from the mITT analysis set because IgG data were unavailable at day 29
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; ANCOVA, analysis of covariance; EFG, efgartigimod; IgG, immunoglobulin gamma; IV, intravenous; LS, least squares; mITT, modified intent-to-treat analysis set; N, number of subjects per arm that were included in the ANCOVA analysis; PP, per protocol analysis set; SC, subcutaneous

Reviewer's comment: As noted in Sections 6.2.1.1 and 6.2.1.3, (b) (4) [redacted]

Efficacy Results – Secondary endpoints

The secondary efficacy endpoints were summarized descriptively.

1. Absolute values, change from baseline, and percent reduction from baseline in total IgG levels over time

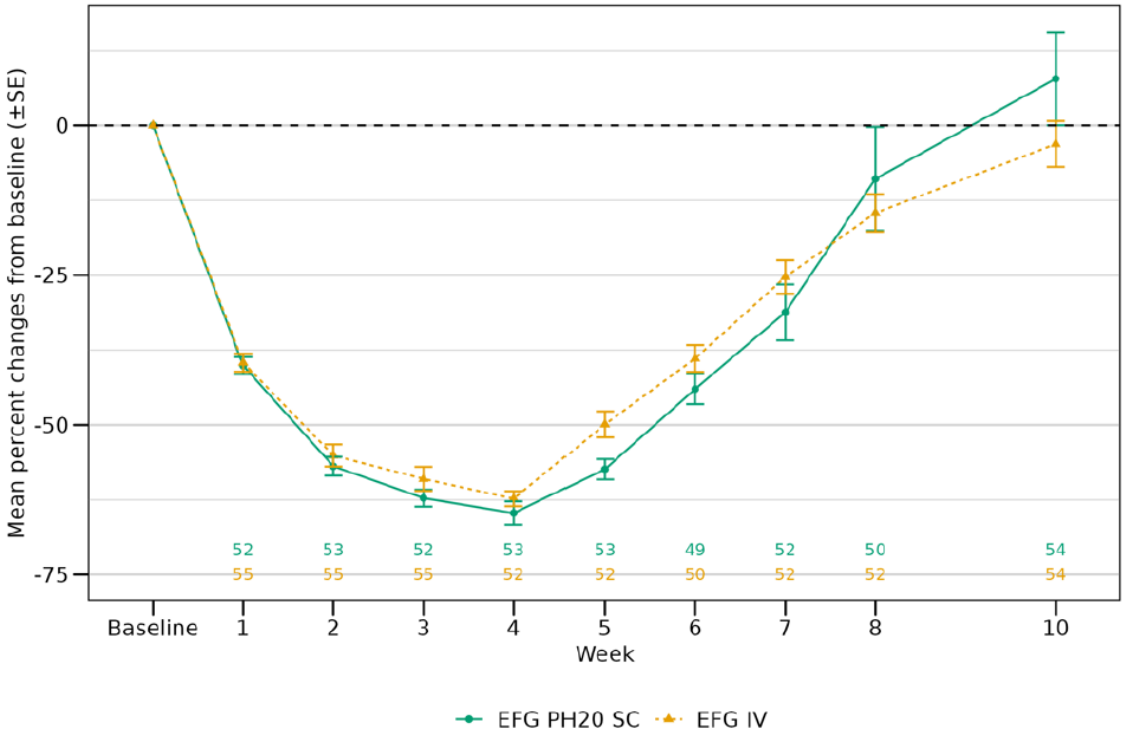
   The percent change from baseline in total IgG levels over time for the overall population in the mITT analysis set is summarized in the following table and figure that were copied from the submission. Reductions in total IgG over time were similar between the efgartigimod PH20 SC arm and IV arm.

Table 10. Total IgG Level Percent Change From Baseline Over Time for the Overall Population (mITT Analysis Set)

	EFG PH20 SC (N=55)		EFG IV (N=55)		EFG PH20 SC vs EFG IV	
Visit	n	Mean (SE)	n	Mean (SE)	Mean	95% CI
Week 1	52	−40.1 (1.45)	55	−39.6 (1.51)	−0.5	−4.63 to 3.66
Week 2	53	−56.9 (1.57)	55	−55.1 (1.85)	−1.8	−6.57 to 3.05
Week 3	52	−62.2 (1.41)	55	−59.0 (2.00)	−3.2	−8.04 to 1.68
Week 4	53	−64.7 (1.95)	52	−62.3 (1.24)	−2.4	−6.98 to 2.20
Week 5	53	−57.4 (1.70)	52	−49.9 (2.17)	−7.5	−13.03 to −2.07
Week 6	49	−44.0 (2.52)	50	−38.9 (2.24)	−5.1	−11.79 to 1.58
Week 7	52	−31.2 (4.67)	52	−25.3 (2.78)	−5.9	−16.71 to 4.92
Week 8	50	−8.9 (8.65)	52	−14.6 (3.13)	5.6	−12.76 to 24.02
Week 10	54	7.8 (7.78)	54	−3.1 (3.82)	10.9	−6.31 to 28.19

Source: Study 2001 CSR, table 31.
Abbreviations: EFG, efgartigimod; IgG, immunoglobulin gamma; IV, intravenous(ly); mITT, modified intent-to-treat; N, number of subjects per arm in the analysis set; n, number of subjects for whom the observation was reported; SC, subcutaneous

Figure 7. Total IgG Level Percent Change From Baseline Over Time for the Overall Population (mITT Analysis Set)



Source: Study 2001 CSR, figure 11.
Abbreviations: EFG, efgartigimod (PH20); IgG, immunoglobulin gamma; IV, intravenous; mITT, modified intent-to-treat; SC, subcutaneous

2. Absolute values, change from baseline, and percent reduction from baseline in anti-acetylcholine receptor antibody (AChR-Ab) levels over time in AChR-Ab seropositive subjects

   The percent change from baseline in AChR-Ab levels over time for the AChR-Ab seropositive population in the mITT analysis set is summarized in the following table and figure that were copied from the submission. The percent change from baseline at week 4 in AChR-Ab levels was -62% in the efgartigimod PH20 SC arm and -59% in the efgartigimod IV arm. The mean percent change from baseline over time in AChR-Ab levels for the AChR-Ab seropositive population was similar between both arms.

Table 11. AChR-Ab Levels Percent Change From Baseline Over Time in (mITT Analysis Set)

	EFG PH20 SC (N=45)		EFG IV (N=46)		EFG PH20 SC vs EFG IV	
Visit	**n**	**Mean (SE)**	**n**	**Mean (SE)**	**Mean**	**95% CI**
Week 1	43	−42.5 (1.50)	45	−43.7 (1.55)	1.2	−3.07 to 5.50
Week 2	43	−57.4 (1.39)	45	−55.1 (1.52)	−2.4	−6.46 to 1.73
Week 3	42	−61.8 (1.60)	45	−59.2 (1.66)	−2.6	−7.18 to 1.99
Week 4	44	−62.2 (1.76)	42	−59.6 (1.74)	−2.6	−7.50 to 2.35
Week 5	43	−55.3 (1.52)	43	−47.2 (2.98)	−8.0	−14.72 to −1.35
Week 6	40	−40.4 (3.13)	41	−29.9 (4.61)	−10.5	−21.61 to 0.64
Week 7	42	−26.7 (4.76)	43	−15.8 (5.63)	−10.9	−25.58 to 3.76
Week 8	40	−14.5 (7.82)	43	−7.1 (6.02)	−7.4	−27.02 to 12.29
Week 10	44	13.5 (23.16)	44	10.3 (7.85)	3.2	−45.88 to 52.22

Source: Study 2001 CSR, table 35
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; IgG, immunoglobulin gamma; IV, intravenous(ly); mITT, modified intent-to-treat; N, number of subjects per arm in the analysis set; n, number of subjects for whom the observation was reported; SC, subcutaneous(ly)

3. Absolute values, change from baseline, and percent reduction from baseline in IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time.

   The median (interquartile range) percent change from baseline at week 4 and AUEC percent change from baseline over the study duration (baseline to week 10) for the IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) in the overall population of the mITT analysis set is summarized in the following table, copied from the submission. The pattern of total IgG level and IgG subtype reduction over time was similar in the efgartigimod PH20 SC and IV arms.

Table 12. Median (IQR) Percent Change From Baseline and AUEC for the Percent Change From Baseline for the IgG Subtypes in the Overall Population (mITT Analysis Set)

	EFG PH20 SC (N=55)		EFG IV (N=55)	
	n	Median (Q1; Q3)	n	Median (Q1; Q3)
Percent change from baseline at week 4				
IgG1	43	−71.0 (−79.3 to −56.6)	35	−68.4 (−73.0 to −61.5)
IgG2	43	−65.6 (−72.2 to −58.1)	35	−64.5 (−73.0 to −57.4)
IgG3	43	−69.6 (−78.3 to −58.4)	35	−64.7 (−76.9 to −59.5)
IgG4	43	−56.4 (−64.4 to −37.2)	35	−55.5 (−64.2 to −42.1)
AUEC for percent change from baseline (baseline – week 10)				
IgG1	35	−3054.1 (−3679.2 to −1933.1)	33	−2935.2 (−3195.0 to −2422.0)
IgG2	35	−2709.9 (−3551.5 to −1932.2)	33	−2796.3 (−3187.9 to −2076.3)
IgG3	35	−2732.9 (−3437.9 to −1602.7)	33	−2566.5 (−3567.4 to −1973.9)
IgG4	35	−2060.5 (−2815.7 to −874.3)	33	−1979.4 (−2730.6 to −1160.1)

Source: Study 2001 CSR, table 34.
Note: AUEC shown are in % × days.
Abbreviations: AUEC, area under the effect curve; EFG, efgartigimod; IgG, immunoglobulin; IQR, interquartile range; IV, intravenous(ly); mITT, modified intent-to-treat; N, number of subjects with data available; n, number of subjects for whom the observation was reported; Q, quartile; SC, subcutaneous(ly)

4. AUEC of the percent reduction from baseline total IgG and similar AUEC for each IgG subtype per dosing interval (days 1-8, days 8-15, days 15-22, and days 22-29), days 1-29, and over the entire study (days 1-71)

   AUEC of the percent change from baseline in total IgG level for the overall population in the mITT analysis set is summarized in the following table, copied from the submission. In the overall population, AUEC of the percent reduction in total IgG level after efgartigimod PH20 SC was similar to efgartigimod IV at each intermediate interval and over the duration of the study.

Table 13. AUEC of the Percent Change From Baseline in Total IgG Level for the Overall Population (mITT Analysis Set)

	EFG PH20 SC (N=55)		EFG IV (N=55)	
Interval	**n**	**Mean (SE)**	**n**	**Mean (SE)**
Days 1-8 (baseline-week 1)	52	−138.9 (5.48)	55	−139.1 (5.67)
Days 8-15 (week 1-week 2)	52	−341.9 (9.90)	55	−328.3 (10.98)
Days 15-22 (week 2-week 3)	51	−416.0 (12.06)	55	−399.8 (14.46)
Days 22-29 (week 3-week 4)	50	−447.3 (9.24)	52	−427.0 (9.76)
Days 1-29 (baseline-week 4)	51	−1332.5 (30.78)	52	−1311.6 (26.35)
Days 1-57 (baseline-week 8)	49	−2515.9 (96.98)	51	−2387.6 (77.61)
Days 1-71 (baseline-week 10)	52	−2562.9 (171.86)	52	−2500.3 (116.10)

Source: Study 2001 CSR, table 33.
Note: AUEC shown are in % × days.
Abbreviations: AUEC, area under the effect curve; EFG, efgartigimod; IgG, immunoglobulin gamma; IV, intravenous(ly); mITT, modified intent-to-treat; N, number of subjects with data available; n, number of subjects for whom the observation was reported; SC, subcutaneous(ly)

5. PK parameters: maximum concentration (C_{max}) (after all doses for the IV treatment arm) and concentration observed predose (C_{trough}) (after all doses for the IV and SC treatment arms)

   After each efgartigimod PH20 SC administration, C_{trough} was 50% to 60% higher compared with efgartigimod IV. Mean standard deviation (SD) C_{trough} after efgartigimod PH20 SC administration ranged between 18.3 (8.05) µg/mL and 22.5 (8.12) µg/mL. After efgartigimod IV administration, peak concentrations were observed at the end of each weekly infusion. Mean (SD) C_{max} remained stable after each infusion, with values ranging from 199 (62.8) to 215 (63.0) µg/mL. Also, mean (SD) C_{trough} remained stable, ranging from 14.0 (6.92) to 16.4 (33.0) µg/mL (Table 14.2.8.3).

6. Incidence and prevalence of ADA against efgartigimod

   Of the 19 (34.5%) ADA positive subjects, 18 (32.7%) subjects were classified as treatment-induced ADA and 1 (1.8%) subject was classified as treatment-boosted ADA. In the efgartigimod IV arm, there were 11 (20.0%) ADA positive subjects, of whom 10 (18.2%) subjects were classified as treatment-induced ADA and 1 (1.8%) subject was classified as treatment-boosted ADA.

   The incidence of ADA against efgartigimod was 34.5% in the efgartigimod PH20 SC arm and 20.0% in the efgartigimod IV arm. The ADA prevalence was 45.5% in the efgartigimod PH20 SC arm and 27.3% in the efgartigimod IV arm.

7. Incidence and prevalence of antibodies against rHuPH20 in the SC treatment arm

   Of the 3 (5.5%) subjects who were positive for antibodies against rHuPH20, 2 (3.6%) subjects had treatment-induced antibodies against rHuPH20 and 1 (1.8%) subject had treatment-boosted antibodies against rHuPH20.

   The incidence of antibodies against rHuPH20 in the efgartigimod PH20 SC arm was 5.5%. The prevalence of antibodies against rHuPH20 was 14.5%.

8. Incidence and severity of adverse events (AEs), incidence of serious AEs (SAEs), and changes in laboratory test results, physical examination results, vital signs, and ECGs results

   See the safety analysis in Section 7.

   There were no clinically meaningful changes from baseline in ECG parameters in the efgartigimod PH20 SC and IV arms.

   Physical examination findings were similar in the efgartigimod PH20 SC and IV arms, except for abnormal findings associated with myasthenia gravis symptoms or localized injection site reactions that were reported more frequently in the efgartigimod PH20 SC arm as described in Section 7.6.1.5.

9. Number and percentage of (MG-ADL) responders

   This study was not powered for clinical efficacy and the results were reported descriptively.

   MG-ADL responders were defined as subjects who had a reduction of ≥2 points from baseline on the MG-ADL score for ≥4 consecutive weeks with the first of these reductions occurring at the latest 1-week after the last administration of investigational medicinal product.

   The percentage of MG-ADL responders was the same for subjects in the efgartigimod PH20 SC and IV arms (38 [69%] subjects each) in the overall population.

   Note that this percentage of responders is similar to the 68% reported in the efgartigimod IV group in the pivotal efficacy study for the approved product Vyvgart (efgartigimod IV).

10. Number and percentage of QMG responders

    This study was not powered for clinical efficacy and the results were reported descriptively.

    QMG responders were defined as subjects who had a reduction of ≥3 points from baseline on the QMG score for ≥4 consecutive weeks, with the first of these reductions occurring at the latest 1-week after the last administration of investigational medicinal product.

    In the overall population, the percentage of QMG responders based on the reported QMG total score was 66% (36 subjects) in the efgartigimod PH20 SC arm and 52% (28 subjects) in the efgartigimod IV arm.

    Note that these percentages of responders are similar to the 63% reported in the efgartigimod IV group in the pivotal efficacy study for the approved product Vyvgart (efgartigimod IV).

11. Change from baseline in MG-ADL total score over time

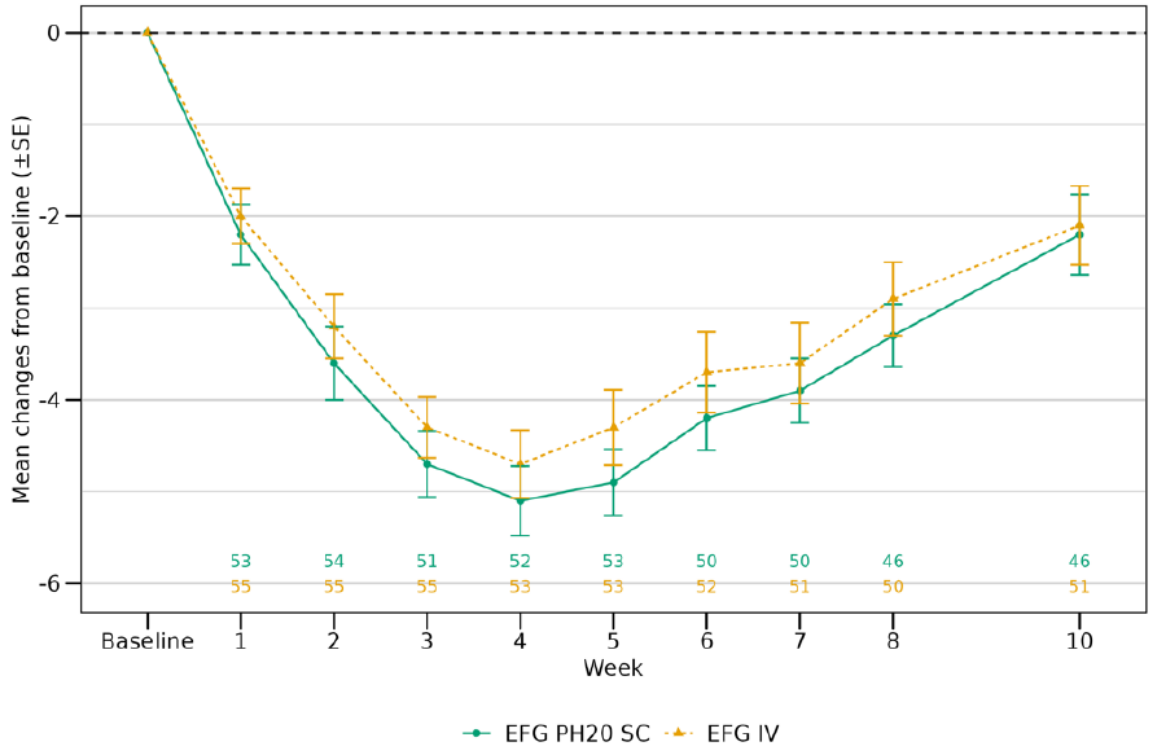
    The mean (SE) change from baseline in MG-ADL total score over time for the overall population in the ITT analysis set is summarized in the following table and figure, copied from the submission.

Table 14. MG-ADL Total Score Change From Baseline Over Time for the Overall Population (ITT Analysis Set)

	EFG PH20 SC (N=55)		EFG IV (N=55)		EFG PH20 SC vs EFG IV	
Visit	**n**	**Mean (SE)**	**n**	**Mean (SE)**	**Mean**	**95% CI**
Week 1	53	−2.2 (0.33)	55	−2.0 (0.30)	−0.2	−1.09 to 0.68
Week 2	54	−3.6 (0.40)	55	−3.2 (0.35)	−0.3	−1.38 to 0.75
Week 3	51	−4.7 (0.36)	55	−4.3 (0.33)	−0.4	−1.38 to 0.58
Week 4	52	−5.1 (0.38)	53	−4.7 (0.37)	−0.4	−1.46 to 0.62
Week 5	53	−4.9 (0.36)	53	−4.3 (0.41)	−0.6	−1.70 to 0.46
Week 6	50	−4.2 (0.35)	52	−3.7 (0.44)	−0.5	−1.61 to 0.63
Week 7	50	−3.9 (0.35)	51	−3.6 (0.44)	−0.3	−1.38 to 0.84
Week 8	46	−3.3 (0.34)	50	−2.9 (0.40)	−0.3	−1.39 to 0.70
Week 10	46	−2.2 (0.44)	51	−2.1 (0.43)	−0.1	−1.35 to 1.11

Source: Study 2001 CSR, table 12.
Abbreviations: EFG, efgartigimod; ITT, intent-to-treat; IV, intravenous(ly); MG-ADL, Myasthenia Gravis Activities of Daily Living; n, number of subjects for whom the observation was reported; N, number of subjects per arm in the analysis set; SC, subcutaneous(ly)

Figure 8. MG-ADL Total Score Change From Baseline Over Time for the Overall Population (ITT Analysis Set)



Source: Study 2001 CSR, figure 2.
Abbreviations: EFG, efgartigimod; ITT, intent-to-treat; IV, intravenous(ly); MG-ADL, Myasthenia Gravis Activities of Daily Living; SC, subcutaneous(ly)

The maximum reduction in MG-ADL total score was at week 4 (1-week after the last injection); the mean change from baseline at week 4 was −5.1 (0.38) versus −4.7 (0.37) ([95% CI: −1.46 to 0.62]) in the efgartigimod PH20 SC and IV arms, respectively.

Note that this pattern of MG-ADL score improvement is similar to that reported in the pivotal study for the approved product Vyvgart (efgartigimod IV).

12. Change from baseline in QMG score over time

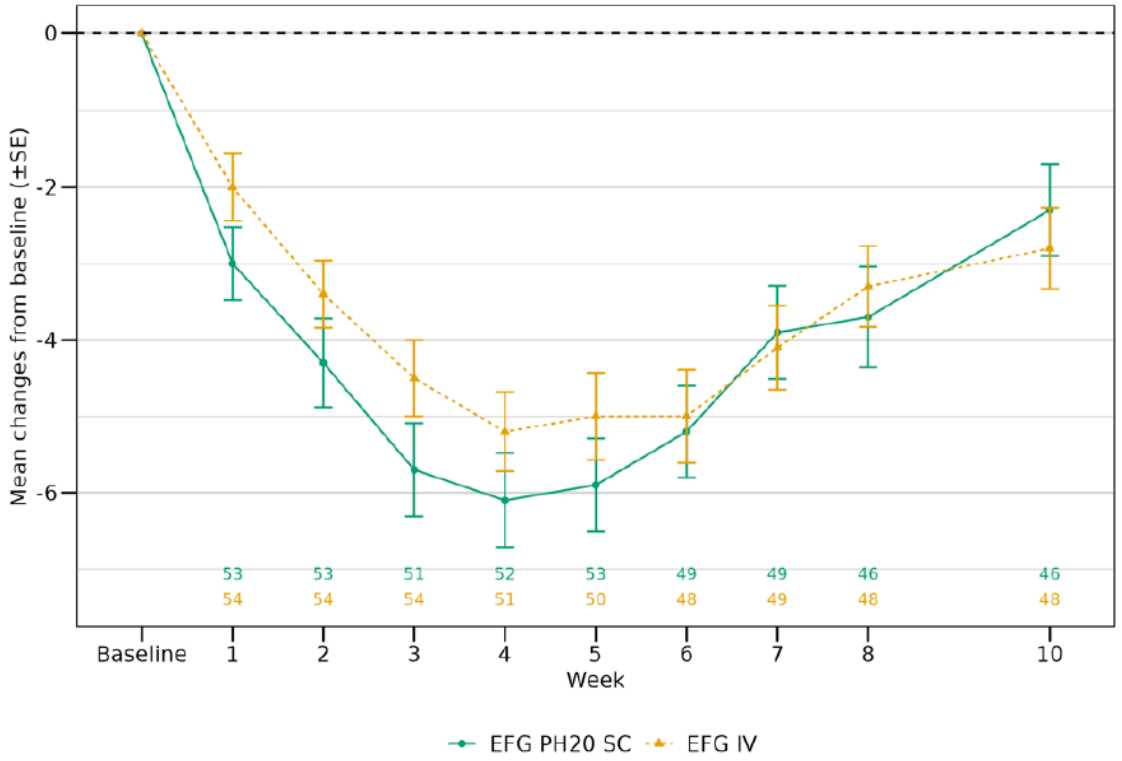
The mean (SE) change from baseline in QMG total score over time for the overall population in the ITT analysis set is summarized in the following table and figure, copied from the submission.

Table 15. QMG Total Score Change From Baseline Over Time for the Overall Population (ITT Analysis Set)

	EFG PH20 SC (N=55)		EFG IV (N=55)		EFG PH20 SC vs EFG IV	
Visit	**n**	**Mean (SE)**	**n**	**Mean (SE)**	**Mean**	**95% CI**
Week 1	53	−3.0 (0.48)	54	−2.0 (0.44)	−0.9	−2.24 to 0.36
Week 2	53	−4.3 (0.58)	54	−3.4 (0.44)	−0.9	−2.36 to 0.54
Week 3	51	−5.7 (0.61)	54	−4.5 (0.50)	−1.2	−2.80 to 0.32
Week 4	52	−6.1 (0.62)	51	−5.2 (0.52)	−0.9	−2.46 to 0.74
Week 5	53	−5.9 (0.61)	50	−5.0 (0.57)	−1.0	−2.62 to 0.69
Week 6	49	−5.2 (0.60)	48	−5.0 (0.61)	−0.2	−1.94 to 1.45
Week 7	49	−3.9 (0.61)	49	−4.1 (0.55)	0.3	−1.36 to 1.89
Week 8	46	−3.7 (0.66)	48	−3.3 (0.53)	−0.4	−2.12 to 1.27
Week 10	46	−2.3 (0.60)	48	−2.8 (0.53)	0.5	−1.10 to 2.07

Source: Study 2001 CSR, table 15.
Abbreviations: EFG, efgartigimod; IV, intravenous(ly); ITT, intent-to-treat; n, number of subjects for whom the observation was reported; N, number of subjects per arm in the analysis set; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous(ly)

Figure 9. QMG Total Score Change From Baseline Over Time for the Overall Population (ITT Analysis Set)



Source: Study 2001 CSR, figure 8.
Abbreviations: EFG, efgartigimod; IV, intravenous(ly); ITT, intent-to-treat; n, number of subjects for whom the observation was reported; N, number of subjects per arm in the analysis set; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous(ly)

The maximum reduction in QMG total score was at week 4; the mean (SE) change from baseline in QMG total score at week 4 was −6.1 (0.62) versus −5.2 (0.52) in the efgartigimod PH20 SC and IV arms, respectively.

Note that this pattern of QMG score improvement is similar to that reported in the pivotal study for the approved product Vyvgart (efgartigimod IV).

6.3. Key Efficacy Review Issues

6.3.1. Evaluation of Bridging Strategy Utilizing Acetylcholine Receptor-Antibody (AChR-Ab) Plasma Levels

Is the Bridging Strategy Utilizing Acetylcholine Receptor-Antibody (AChR-Ab) Plasma Levels Sufficient to Support Effectiveness of Vyvgart Hytrulo for the Treatment of gMG?

Issue and Background:

Although the PK-based bridging approach with standard bioequivalence criteria is commonly used for comparability assessment across products with same active ingredient, this approach is

not applicable to the proposed efgartigimod PH20 SC product in comparison to the efgartigimod IV product because of the differences in PK profiles between the IV and SC administration. The mean C_{max} and $AUC_{0\text{-}168h}$ after the fourth efgartigimod administration were approximately 78% and 16% lower following treatment with efgartigimod PH20 SC 1008 mg compared to efgartigimod IV 10 mg/kg, respectively (Refer to Figure 16 in Appendix 14.2.1, Study 1907), and the AUC was not demonstrated to be bioequivalent between IV and SC formulations for all the body weights. Instead, comparability was established using serum AChR-Ab as the bridging biomarker to support the approval of efgartigimod PH20 SC for the treatment of gMG. (b) (4) [redacted] Detailed justification of the acceptability of the comparability is discussed below.

Assessment

Comparable reduction in AChR-Ab is considered an appropriate metric for bridging based on clear understanding on (1) the role of AChR-Ab in the disease pathophysiology in gMG; (2) the mechanism of action of efgartigimod; and (3) the clinical and PK/PD data from the efgartigimod IV development program, as described below.

AChR-Ab level is mechanistically relevant to the disease pathophysiology of gMG. (Gilhus et al. 2019) Around 80% to 85% of patients with gMG have autoantibodies against the AChR, which induce pathogenicity by various mechanisms. (Koneczny and Herbst 2019) Reduction of AChR-Ab was observed following immunomodulatory therapies for gMG, such as plasma exchange and intravenous immunoglobulin. (Wang et al. 2022) AChR-Ab plasma levels were also correlated with clinical response based on data from previous clinical development programs including data for efgartigimod IV product. Hence, the reduction of AChR-Ab by a drug with a well understood mechanism of action that targets the clearance of these antibodies through FcRn receptors justifies the use of AChR-Ab plasma levels as an intermediate endpoint to support the registration of Vyvgart Hytrulo.

An association between reduction in AChR-Ab levels and improvement in the MG-ADL total score was observed in the Phase 3 study ARGX-113-1704 following intravenous administration of efgartigimod (refer to Section 14.5.1 Pharmacometrics Review Figure 21). The correlation between the reductions of AChR-Ab and MG-ADL was also observed in the open-label study ARGX-113-2001 following both IV and SC administrations (Figure 10). The percent reductions in AChR-Ab levels were consistent with clinical improvements in the MG-ADL total scores and followed a similar time course (Figure 10).

Collectively, the review team concluded that the evidence of the mechanistic relevance between AChR-Ab and disease pathophysiology of gMG, along with the association between AChR-Ab and MG-ADL observed in patients with gMG, demonstrated that AChR-Ab is an appropriate PD biomarker for the context of use, i.e., bridging between different routes of administrations for the treatment of gMG.

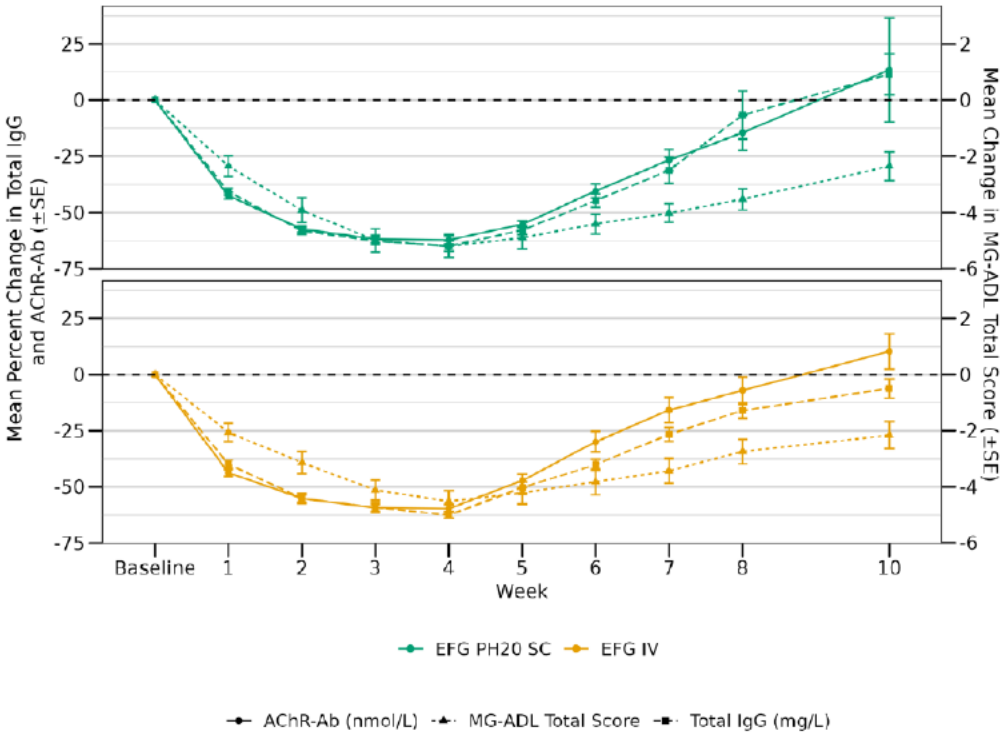
(b) (4) [redacted]

(b) (4)

The review relied mainly on the AChR-Ab data because of its association with the pathophysiology of gMG.

The plasma as a matrix to establish comparable PD profile has been found acceptable because it is believed that the autoantibodies are produced by the plasma cells and will be circulating in the plasma before reaching the neuromuscular junction (i.e., the site of action).

Figure 10. Change in MG-ADL Total Score and Percent Change in Levels of Total IgG and AChR-Ab in AChR-Ab Seropositive Population in Study ARGX-113-2001



Source: Applicant's summary of clinical pharmacology studies, page 45, Figure 15.
Abbreviations: AChR, anti-acetylcholine receptor antibody, IgG, immunoglobulin gamma; MG-ADL, Myasthenia Gravis Activities of Daily Living

6.3.2. Comparability of Reductions in AChR-Ab Between the IV and SC Formulations

Figure 11 shows the percent change from baseline in AChR-Ab levels over time following IV and SC treatment, which suggests that the mean percentage of reduction in AChR-Ab at day 29 was comparable between efgartigimod PH20 SC and IV arm. The maximum reduction in AChR-Ab occurred at week 4. The least-squares mean (LSM) estimate of the percent change from baseline AChR-Ab at day 29 was -62.2% (95% CI: -65.64% to -58.75%) in the efgartigimod PH20 SC arm and -59.7% (95% CI: -63.20% to -56.15%) in the efgartigimod IV arm. Thereafter, in both arms the AChR-Ab levels slowly increased and returned to baseline by the end of the follow-up period at week 10.

Reductions of AChR-Ab following IV and SC treatment are summarized in Table 16. Reviewer's independent analysis confirmed that the 90% CI of geometric mean ratio (GMR) for

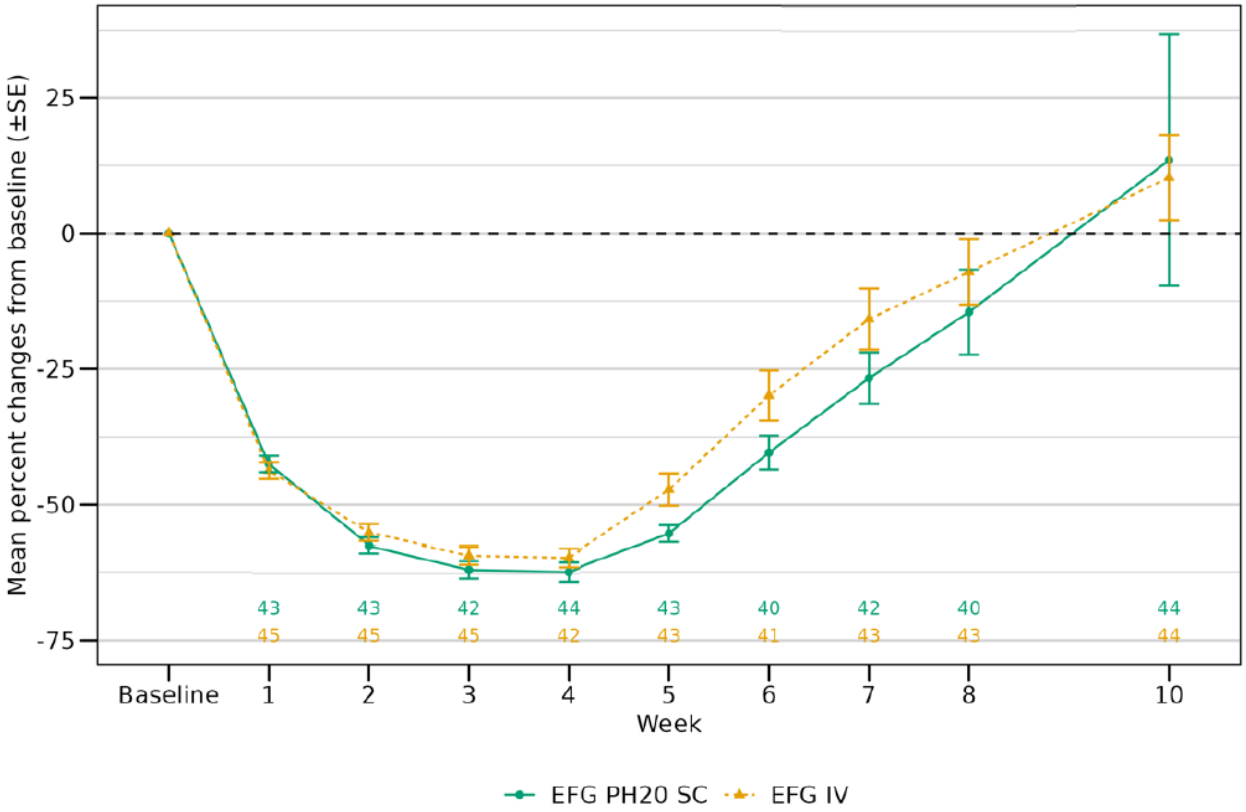
the PD metrics (percentage of reduction at day 29 and AUEC 0 to 4 weeks) were contained within 80% to 125% margin (refer to Section 14.5.2 Pharmacometrics Review). In addition, the Applicant's analysis showed that the upper limit of the 95% CI of LSM difference in AChR-Ab percent of change from baseline at day 29 between IV versus SC (2.41%) was below the prespecified non-inferiority margin of 10%.

The reviewer noted the imbalance of baseline AChR-Ab level between IV and SC treatment groups in Table 16. In an information request (IR) response submitted on January 17, 2023, the Applicant explained that the imbalance was driven by an observation from a single subject in the IV treatment arm (i.e., (b) (6)), who had an extremely high AChR-Ab value at baseline (i.e., 1540 nmol/L). This subject had no PD data available after week 3 and does not impact the comparison of AChR-Ab on day 29. Reviewer's analysis showed that the profiles of AChR-Ab reduction over time were similar with or without the outlier subject (Refer to Section 14.5.2 Pharmacometrics Review).

The reviewer also conducted sensitivity analysis for the percent change in AChR-Ab on day 29 to evaluate the impact of (1) the six subjects who had missing doses; and (2) the samples with actual value lower than the lower limit of quantification 0.256 ng/mL, but was imputed as 0.256 ng/mL, which suggest that the comparability of AChR-Ab percent reduction on day 29 remains unaffected after removing the subjects with missing doses or removing the imputed samples. (Refer to Section 14.5.2 Pharmacometrics Review)

The serum AChR-Ab level in Study 2001 was quantified using a commercialized kit with a radioimmunoassay (RIA) method. The bioanalytical method was validated by the Applicant. Overall, the method for analyzing the serum AChR-Ab was adequate to support the bridging using this PD biomarker. Please refer to Appendix 14.3.2 for additional details.

Figure 11. Percent Change From Baseline in AChR-Ab Levels Over Time in the AChR-Ab Seropositive Population



Source: Applicant's summary of clinical pharmacology studies, page 25, Figure 7.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; IV, intravenous

Table 16. Summary of AChR-Ab Parameters After 4 Once-Weekly Administrations of Efgartigimod PH20 SC 1008 mg or Efgartigimod IV 10 mg/kg in AChR-Ab Seropositive Subjects With gMG

	Efgartigimod PH20 SC 1000 mg		Efgartigimod IV 10 mg/kg		GMR (90% CI)
	n	Mean (SE)	n	Mean (SE)	
Baseline (nmol/L)	45	48.2 (15.9)	46	74.8 (34.2)	NA
Reduction at day 29 (%)	44	62.2 (1.76)	42	59.6 (1.74)	1.05 (0.93–1.18)
E_{max} (%)	45	63.8 (1.43)	45	60.8 (1.67)	1.07 (0.98–1.17)
$AUEC_{0\text{-}1w}$ (%.days)	43	149 (5.74)	45	154 (5.95)	0.93 (0.86–1.02)
$AUEC_{3\text{-}4w}$ (%.days)	41	440 (10.5)	42	417 (11.0)	1.06 (0.99–1.14)
$AUEC_{0\text{-}4w}$ (%.days)	42	1359 (30.2)	42	1329 (27.9)	1.02 (0.97–1.08)
$AUEC_{0\text{-}8w}$ (%.days)	39	2465 (96.9)	42	2230 (135)	1.00 (0.83–1.21)
AUEC (%.days)	42	2353 (426)	43	2173 (228)	1.11 (1.01–1.23)

Source: Applicant's summary of clinical pharmacology studies, page 26, Table 7.
AUECx-yw = area under the effect curve for percentage reduction compared with baseline over the interval week x to y
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody positive; AUEC, area under the effect curve; E_{max}, maximum percentage reduction compared with baseline; gMG, generalized myasthenia gravis; GMR, geometric mean ratio; IV, intravenous; SC, subcutaneous.

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Conclusion

The review team concludes that reduction in AChR-Ab is an appropriate metric to support registration of the efgartigimod SC product, and the data analysis demonstrated comparable reduction of AChR-Ab between IV and SC formulations. (b) (4)

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The results of the nonclinical studies submitted to support the SC formulation did not identify any new safety concerns and are adequate to bridge to the existing IV data.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Efgartigimod is a neonatal Fc receptor blocker. The known risks associated with the IV form (efgartigimod alfa-fcab injection/Vyvgart) are described in the approved labeling include infections and hypersensitivity reactions, which are discussed further in Section 7.7. The most common adverse reactions (ARs) (≥10%) in subjects treated with Vyvgart for gMG are respiratory tract infections, headache, and urinary tract infection.

Hylenex recombinant (hyaluronidase human injection) is a tissue permeability modifier. The known risks associated with Hylenex and described in the approved labeling include spread of localized infection, ocular damage (if applied directly to the cornea), and enzyme inactivation with intravenous administration (Hylenex cannot affect tissue permeability if administered intravenously because it is rapidly inactivated). Allergic and anaphylactic-like reactions have been reported rarely.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

As of March 31, 2022, approximately (b) (4) subjects in the United States had been treated with efgartigimod IV. Based on the postmarketing safety data, no new safety concerns for efgartigimod IV were identified by the Applicant. The FDA's Postmarket Drug Safety Surveillance Summary of March 14, 2023, identified anaphylaxis and infusion-related reactions as new safety signals. The Division of Pharmacovigilance will follow CDER's Newly Identified Safety Signal process to determine whether anaphylaxis and infusion-related reactions warrant further evaluation.

Adverse reactions have been identified during post-approval use of hyaluronidase products. The most frequently reported ARs have been mild local injection site reactions such as erythema and pain. Hyaluronidase has been reported to enhance the ARs associated with co-administered drug products. Edema has been reported most frequently in association with subcutaneous fluid administration. Allergic reactions (urticaria or angioedema) have been reported in less than 0.1% of subjects receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred, rarely.

7.4. FDA Approach to the Safety Review

Clinical study data were independently analyzed using JMP software. Additional analyses were provided by the clinical data scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. No major data quality or integrity issues were identified that would preclude a safety review of this BLA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in Studies 2001 and 2002 were reviewed and found to be acceptable. All AEs in the reviewed trials were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5).

Data from the completed randomized, open-label, parallel-group Study 2001 and from the ongoing open-label extension Study 2002 formed the basis of the clinical safety evaluation, as well as additional supportive safety data from subjects who transitioned from the supportive open-label extension Study 1705 from the approved IV form of efgartigimod into Study 2002.

A summary of the study designs can be found in Section 3.2 and Section 6.2.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of efgartigimod/rHuPH20 SC for the proposed indication, patient population, dosage regimen, and duration. In Type C Guidance under investigational new drug (IND) 132953 dated December 4, 2020, the Division advised the Applicant that the safety database for the SC administration of efgartigimod should include 100 subjects with gMG treated for 6 months and should include immunogenicity assessments. The overall number of exposed subjects (168 total: 55 in Study 2001, 48+65 IV-SC in Study 2002 from the following two tables for efgartigimod/rHuPH20 SC) is adequate in terms of size and dosing. One hundred six subjects have at least 6 months of efgartigimod SC exposure.

Table 18. Duration of Exposure, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001		ARGX-113-2002		
Parameter	EFG SC N=55 n (%)	EFG IV N=55 n (%)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Duration of treatment, days					
Mean (SD)	85.4 (8.4)	84.9 (4.3)	159.6 (50.7)	165 (49.1)	162.2 (49.7)
Median (Q1, Q3)	85 (84, 85.5)	85 (85, 85)	177 (108.5, 204)	178 (144.5, 203.2)	178 (113.5, 204)

	ARGX-113-2001		ARGX-113-2002		
Parameter	EFG SC N=55 n (%)	EFG IV N=55 n (%)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Min, Max	56, 135	58, 92	71, 241	67, 282	67, 282
Total exposure (person years)	13	13	22	22	44
Subjects treated, by duration, n (%)					
<60 days	1 (1.8)	1 (1.8)	0	0	0
≥60 to <80 days	3 (5.5)	1 (1.8)	1 (2.0)	1 (2.1)	2 (2.0)
≥80 to <100 days	50 (90.9)	53 (96.4)	11 (21.6)	9 (18.8)	20 (20.2)
≥100 to <130 days	0	0	4 (7.8)	1 (2.1)	5 (5.1)
≥130 to <160 days	1 (1.8)	0	6 (11.8)	6 (12.5)	12 (12.1)
≥160 to <200 days	0	0	13 (25.5)	18 (37.5)	31 (31.3)
≥200 days	0	0	16 (31.4)	13 (27.1)	29 (29.3)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Abbreviations: EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Table 19: Duration of Exposure, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Parameter	IV-SC (1705) N=65 n (%)
Duration of treatment, days	
Mean (SD)	181.1 (69.3)
Median (Q1, Q3)	189 (154, 218)
Min, Max	24, 311
Total exposure (person years)	32
Subjects treated, by duration, n (%)	
<60 days	6 (9.2)
≥60 to <80 days	1 (1.5)
≥80 to <100 days	2 (3.1)
≥100 to <130 days	3 (4.6)
≥130 to <160 days	7 (10.8)
≥160 to <200 days	25 (38.5)
≥200 days	21 (32.3)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 2 years.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Studies 2001 and 2002

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of adverse events for the completed randomized, open-label, parallel-group Study 2001 and from the ongoing open-label extension Study 2002 are shown in the following table. Note that this pool includes only subjects rolled over from Study 2001 to 2002. The Study 2002 subset of subjects rolled over from the open-label extension study of the original efgartigimod IV BLA 761195 is described separately in Section 7.6.2.

As seen in the following table, there were more AEs, SAEs, and permanent dose discontinuation due to AEs in the efgartigimod/rHuPH20 SC group than in the efgartigimod IV group. In Study 2001 the proportion of subjects experiencing AEs was 67% in the efgartigimod (EFG) SC group and 51% in the EFG IV group. The proportion experiencing SAEs was 15% in the EFG SC group and 7% in the EFG IV group. Permanent dose discontinuation due to AEs occurred in 4% in the EFG SC group and 0% in the EFG IV group. Once subjects who had received EFG IV in Study 2001 rolled over into Study 2002 and switched to EFG SC, their respective rates of AEs, SAEs, and permanent dose discontinuation due to AEs increased.

Table 20. Overview of Adverse Events, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Event Category	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
SAE	8 (14.5)	4 (7.3)	7.3 (-4.3, 18.8)	8 (15.7)	5 (10.4)	13 (13.1)
SAEs with fatal outcome	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Life-threatening SAEs	0	0	0 (0, 0)	1 (2.0)	1 (2.1)	2 (2.0)
AE leading to permanent discontinuation of study drug	2 (3.6)	0	3.6 (-1.3, 8.6)	0	1 (2.1)	1 (1.0)
AE leading to dose modification of study drug	1 (1.8)	0	1.8 (-1.7, 5.3)	4 (7.8)	7 (14.6)	11 (11.1)
AE leading to interruption of study drug	1 (1.8)	0	1.8 (-1.7, 5.3)	4 (7.8)	7 (14.6)	11 (11.1)
AE leading to reduction of study drug	0	0	0 (0, 0)	0	0	0
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0	0
Other	0	0	0 (0, 0)	0	0	0

	ARGX-113-2001			ARGX-113-2002		
Event Category	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Any AE	37 (67.3)	28 (50.9)	16.4 (-1.8, 34.5)	41 (80.4)	35 (72.9)	76 (76.8)
Severe and worse	9 (16.4)	4 (7.3)	9.1 (-2.9, 21.0)	7 (13.7)	6 (12.5)	13 (13.1)
Moderate	9 (16.4)	6 (10.9)	5.5 (-7.3, 18.2)	20 (39.2)	14 (29.2)	34 (34.3)
Mild	19 (34.5)	18 (32.7)	1.8 (-15.8, 19.5)	14 (27.5)	15 (31.2)	29 (29.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous

7.6.1.2. Deaths, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

There were no deaths in Study 2001. One subject (b) (6) in Study 2002 with a history of prior renal cell cancer 6 years previously was diagnosed with metastatic renal cell cancer 27 days after starting efgartigimod/PH20 SC and died approximately 3 months after the first dose of efgartigimod/PH20 SC. This subject had received efgartigimod IV in Study 2001 before switching to efgartigimod SC in Study 2002. This death was most likely related to the prior history of renal cell cancer.

Table 21. Deaths, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Any AE leading to death	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Renal cancer metastatic	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

Two additional fatal events occurred in the gMG efgartigimod SC clinical program in the 90-day safety update in ARGX-113-2002. One subject (b) (6), a 56-year-old male with a history of hypertension and erosive duodenitis, died of cardiac arrest. The subject had concurrent SAEs of sepsis, respiratory failure following COVID-19, and pneumonia. The subject also had an intestinal perforation followed by surgical resection of transverse colon and subsequent peritonitis and sepsis that led to cardiac arrest. The second subject (b) (6), a 70-year-old male with a history of appendectomy, peptic ulcer perforation, gastrectomy, type 2 diabetes mellitus, and COVID-19 infection, died because of respiratory failure from a pulmonary mass. During ARGX-113-2001, the subject had a grade 1 nonserious AE (PT: pulmonary mass), which was ongoing at the end of the study. The event became serious during cycle 3 of ARGX-113-2002. At the time of the event, the subject had received all 4 doses of efgartigimod IV 10 mg/kg in ARGX-113-2001 from (b) (6), and had received 12 doses

and completed three cycles of efgartigimod PH20 SC 1008 mg in ARGX-113-2002 from (b) (6). Note that the risk of developing lung cancer increases with age and most cases are diagnosed after age 60. These subjects were quite ill, with complex, chronic multisystem diseases and complicated courses. It is not possible to attribute these deaths to efgartigimod; conversely, it is not possible to be confident that the drug was not in some way contributory.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of serious adverse events for Studies 2001 and the subjects who then continued into Study 2002 are shown in the following tables. The proportion of subjects experiencing SAEs was 15% in the EFG PH20 SC group and 7% in the EFG IV group. As seen in the following tables, the only SAE that occurred at least 2% more frequently in the EFG PH20 SC group was myasthenia gravis (i.e., worsening of disease symptoms) in 9% of the EFG PH20 SC group versus 2% of the EFG IV group.

Table 22. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
System Organ Class Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Overall	8 (14.5)	4 (7.3)	7.3 (-4.3, 18.8)	8 (15.7)	5 (10.4)	13 (13.1)
Cardiac disorders (SOC)	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Cardiac failure congestive	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
General disorders and administration site conditions (SOC)	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Chest pain	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Infections and infestations (SOC)	1 (1.8)	0	1.8 (-1.7, 5.3)	1 (2.0)	3 (6.2)	4 (4.0)
Cellulitis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
COVID-19	0	0	0 (0, 0)	0	2 (4.2)	2 (2.0)
COVID-19 pneumonia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Diarrhoea infectious	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Pneumonia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Rotavirus infection	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Injury, poisoning and procedural complications (SOC)	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Humerus fracture	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Rib fracture	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Spinal fracture	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Renal cancer metastatic	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Nervous system disorders (SOC)	6 (10.9)	1 (1.8)	9.1 (0.1, 18.1) *	4 (7.8)	1 (2.1)	5 (5.1)
Myasthenia gravis	5 (9.1)	1 (1.8)	7.3 (-1.1, 15.7)	4 (7.8)	1 (2.1)	5 (5.1)
Optic neuritis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Syncope	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0

	ARGX-113-2001			ARGX-113-2002		
System Organ Class Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Reproductive system and breast disorders (SOC)	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Testicular cyst	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	1 (2.1)	2 (2.0)
Dyspnoea	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	0	1 (1.0)
Respiratory failure	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous; SOC, system organ class

Table 23. Subjects With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Narrow)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Cardiac disorders (SOC)						
Heart failure	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Gastrointestinal disorders (SOC)						
Diarrhea	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Infections and infestations (SOC)						
Bacterial infection	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Pneumonia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Viral infection	0	0	0 (0, 0)	1 (2.0)	3 (6.2)	4 (4.0)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Nervous system disorders (SOC)						
Syncope	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Narrow)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)						
Dyspnea	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	0	1 (1.0)
Respiratory failure	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

The 90-day safety update reported SAEs that occurred in 12 additional subjects in study ARGX-113-2002 who did not have any SAEs in the initial application, summarized in the following table.

Table 24. ARGX-113-2002 – 90-Day Safety Update, Serious Adverse Events

Subject Number	Serious Adverse Event (Preferred Term, Verbatim)
(b) (6)	SPINAL FRACTURE (BACK FRACTURE)
	DYSPNOEA (WORSENING SHORTNESS OF BREATH)
	CELLULITIS (RIGHT LEG CELLULLITIS)
	MYASTHENIA GRAVIS (WORSENING OF MYASTENIA GRAVIS)
	MYASTHENIA GRAVIS (EXACERBATION MG)
	DIARRHOEA INFECTIOUS (COLONIC INFECTION WITH DIARRHEA); ROTAVIRUS INFECTION
	MYASTHENIA GRAVIS (WORSENING OF MYASTHENIC SYMPTOMS FOLLOWING COVID19 VACCINATION)

Subject Number	Serious Adverse Event (Preferred Term, Verbatim)
(b) (6)	MYASTHENIA GRAVIS (MG BULBAR SYMPTOMPS WORSENING)
	TENDON INJURY (ACHILLES TENDON INJURY)
	ULNAR NERVE INJURY (DAMAGE TO THE ULNAR NERVE)
	MYASTHENIA GRAVIS (MYASTHENIC WORSENING)
	RIB FRACTURE (RIBS FRACTURE V-VIII)

Source: LISTING 16.2.7.2

The only SAE in the 90-day safety update that occurred in more than one subject was myasthenia gravis, which is consistent with the SAEs observed in the initial submission for Study 2002.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of adverse events leading to treatment discontinuation for Studies 2001 and the subjects who then continued into Study 2002 are shown in the following tables. In Study 2001, 2 subjects (4%) in the EFG PH20 SC group had AEs leading to treatment discontinuation (COVID-19 and myasthenia gravis) compared to no subjects in the EFG IV group.

Table 25. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
System Organ Class Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Overall	2 (3.6)	0	3.6 (-1.3, 8.6)	0	1 (2.1)	1 (1.0)
Infections and infestations (SOC)	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
COVID-19	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Renal cancer metastatic	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Nervous system disorders (SOC)	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Myasthenia gravis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous; SOC, system organ class

Table 26. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Narrow)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Infections and infestations (SOC)						
Viral infection	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of treatment-emergent adverse events (TEAEs) for Studies 2001 and the subjects who then continued into Study 2002 are shown in the following tables if there were at least 2 subjects who experienced adverse events in any arms by preferred term (PT), FDA Medical Query (Narrow), and FDA Medical Query (Broad). The proportion of subjects experiencing TEAEs was 67% in the EFG PH20 SC group versus 51% in the EFG IV group. As seen in the table, five TEAEs had risk difference 95% confidence intervals that did not include zero, indicating higher proportions in the EFG PH20 SC group: injection site rash, injection site erythema, injection site pruritus, myasthenia gravis, and injection site bruising. Injection site reactions are further discussed in Section 7.7.3.

Table 27. Subjects With Common Adverse Events Occurring at ≥3.6% (2 subjects) Frequency, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Any AE	37 (67.3)	28 (50.9)	16.4 (-1.8, 34.5)	41 (80.4)	35 (72.9)	76 (76.8)
Injection site rash	8 (14.5)	0	14.5 (5.2, 23.9) *	4 (7.8)	5 (10.4)	9 (9.1)
Injection site erythema	7 (12.7)	0	12.7 (3.9, 21.5) *	11 (21.6)	12 (25.0)	23 (23.2)
Injection site pruritus	5 (9.1)	0	9.1 (1.5, 16.7) *	5 (9.8)	3 (6.2)	8 (8.1)
Myasthenia gravis	6 (10.9)	1 (1.8)	9.1 (0.1, 18.1) *	4 (7.8)	1 (2.1)	5 (5.1)
Injection site bruising	4 (7.3)	0	7.3 (0.4, 14.1) *	5 (9.8)	2 (4.2)	7 (7.1)
Injection site pain	3 (5.5)	0	5.5 (-0.5, 11.5)	4 (7.8)	3 (6.2)	7 (7.1)

	ARGX-113-2001			ARGX-113-2002		
Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Abdominal discomfort	2 (3.6)	0	3.6 (-1.3, 8.6)	0	0	0
Abdominal pain upper	2 (3.6)	0	3.6 (-1.3, 8.6)	0	1 (2.1)	1 (1.0)
COVID-19	2 (3.6)	0	3.6 (-1.3, 8.6)	7 (13.7)	4 (8.3)	11 (11.1)
Hypokalemia	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	0	1 (1.0)
Injection site urticaria	2 (3.6)	0	3.6 (-1.3, 8.6)	2 (3.9)	0	2 (2.0)
Migraine	2 (3.6)	0	3.6 (-1.3, 8.6)	0	1 (2.1)	1 (1.0)
Pain in extremity	2 (3.6)	0	3.6 (-1.3, 8.6)	2 (3.9)	0	2 (2.0)
Pharyngitis	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	0	1 (1.0)
Pyrexia	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	2 (4.2)	3 (3.0)
Syncope	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	0	1 (1.0)
Arthralgia	1 (1.8)	0	1.8 (-1.7, 5.3)	3 (5.9)	0	3 (3.0)
Hematuria	1 (1.8)	0	1.8 (-1.7, 5.3)	0	2 (4.2)	2 (2.0)
Hypertension	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	1 (2.0)	1 (2.1)	2 (2.0)
Muscle spasms	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	1 (2.1)	3 (3.0)
Myalgia	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Activated partial thromboplastin time prolonged	0	0	0 (0, 0)	0	2 (4.2)	2 (2.0)
Anemia	0	0	0 (0, 0)	3 (5.9)	1 (2.1)	4 (4.0)
Back pain	0	0	0 (0, 0)	3 (5.9)	3 (6.2)	6 (6.1)
Dry eye	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Dry throat	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Gastroenteritis	0	0	0 (0, 0)	3 (5.9)	0	3 (3.0)
Gastroenteritis viral	0	0	0 (0, 0)	0	2 (4.2)	2 (2.0)
Headache	7 (12.7)	7 (12.7)	0 (-12.5, 12.5)	12 (23.5)	2 (4.2)	14 (14.1)
Influenza like illness	0	0	0 (0, 0)	0	4 (8.3)	4 (4.0)
Injection site mass	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Injection site reaction	0	0	0 (0, 0)	0	2 (4.2)	2 (2.0)
Injection site swelling	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)
Nasopharyngitis	0	0	0 (0, 0)	3 (5.9)	2 (4.2)	5 (5.1)
Neck pain	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)
Oedema	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Oropharyngeal pain	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	2 (3.9)	0	2 (2.0)
Pruritus	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)
Tachycardia	0	0	0 (0, 0)	0	2 (4.2)	2 (2.0)
Type 2 diabetes mellitus	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Upper respiratory tract infection	0	0	0 (0, 0)	4 (7.8)	2 (4.2)	6 (6.1)
Cough	0	1 (1.8)	-1.8 (-5.3, 1.7)	3 (5.9)	1 (2.1)	4 (4.0)
Dizziness	0	1 (1.8)	-1.8 (-5.3, 1.7)	2 (3.9)	0	2 (2.0)
Fatigue	2 (3.6)	3 (5.5)	-1.8 (-9.6, 6.0)	0	4 (8.3)	4 (4.0)
Injection site hematoma	0	1 (1.8)	-1.8 (-5.3, 1.7)	3 (5.9)	2 (4.2)	5 (5.1)
Pneumonia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)
Vaccination complication	0	1 (1.8)	-1.8 (-5.3, 1.7)	2 (3.9)	2 (4.2)	4 (4.0)
Vomiting	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)
Diarrhea	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	5 (9.8)	4 (8.3)	9 (9.1)
Fall	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	1 (2.0)	1 (2.1)	2 (2.0)

	ARGX-113-2001			ARGX-113-2002		
Preferred Term	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Nausea	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	3 (6.2)	4 (4.0)
Urinary tract infection	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	1 (2.0)	0	1 (1.0)
Contusion	0	3 (5.5)	-5.5 (-11.5, 0.5)	3 (5.9)	0	3 (3.0)

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

The following table shows TEAEs that are grouped together using the FDA Medical Query (Narrow). As seen in the table, three TEAEs had risk difference 95% confidence intervals that did not include zero, indicating higher proportions in the EFG PH20 SC group: local administration reaction, nasopharyngitis, and erythema.

Table 28. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Narrow)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Blood and lymphatic system disorders (SOC)						
Anemia	1 (1.8)	0	1.8 (-1.7, 5.3)	3 (5.9)	2 (4.2)	5 (5.1)
Thrombocytopenia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Cardiac disorders (SOC)						
Systemic hypertension	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	2 (3.9)	1 (2.1)	3 (3.0)
Arrhythmia	0	0	0 (0, 0)	0	3 (6.2)	3 (3.0)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	3 (6.2)	3 (3.0)
Heart failure	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	0	0	0
Tachycardia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)
Ear and labyrinth disorders (SOC)						
Vertigo	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	0	1 (1.0)
Endocrine disorders (SOC)						
Hyperglycemia	0	0	0 (0, 0)	3 (5.9)	1 (2.1)	4 (4.0)
Gastrointestinal disorders (SOC)						
Abdominal pain	4 (7.3)	1 (1.8)	5.5 (-2.3, 13.2)	1 (2.0)	1 (2.1)	2 (2.0)
Dry mouth	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Dyspepsia	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	0	2 (4.2)	2 (2.0)
Pancreatitis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Vomiting	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)
Diarrhea	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	5 (9.8)	4 (8.3)	9 (9.1)
Nausea	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	3 (6.2)	4 (4.0)

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Narrow)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
General disorders and administration site conditions (SOC)						
Local administration reaction	21 (38.2)	3 (5.5)	32.7 (18.6, 46.9) *	23 (45.1)	18 (37.5)	41 (41.4)
Pyrexia	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	2 (4.2)	3 (3.0)
Peripheral edema	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	1 (2.0)	0	1 (1.0)
Fatigue	3 (5.5)	3 (5.5)	0 (-8.5, 8.5)	0	5 (10.4)	5 (5.1)
Dizziness	1 (1.8)	2 (3.6)	-1.8 (-7.9, 4.3)	3 (5.9)	0	3 (3.0)
Fall	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	1 (2.0)	1 (2.1)	2 (2.0)
Infections and infestations (SOC)						
Nasopharyngitis	4 (7.3)	0	7.3 (0.4, 14.1) *	8 (15.7)	4 (8.3)	12 (12.1)
Fungal infection	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Pneumonia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)
Viral infection	2 (3.6)	3 (5.5)	-1.8 (-9.6, 6.0)	10 (19.6)	9 (18.8)	19 (19.2)
Bacterial infection	2 (3.6)	5 (9.1)	-5.5 (-14.5, 3.6)	3 (5.9)	2 (4.2)	5 (5.1)
Metabolism and nutrition disorders (SOC)						
Lipid disorder	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)
Musculoskeletal and connective tissue disorders (SOC)						
Arthralgia	1 (1.8)	0	1.8 (-1.7, 5.3)	3 (5.9)	0	3 (3.0)
Fracture	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	1 (2.1)	3 (3.0)
Myalgia	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Arthritis	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Back pain	0	0	0 (0, 0)	3 (5.9)	3 (6.2)	6 (6.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Nervous system disorders (SOC)						
Syncope	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	0	1 (1.0)
Headache	9 (16.4)	9 (16.4)	0 (-13.8, 13.8)	12 (23.5)	3 (6.2)	15 (15.2)
Tremor	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Paresthesia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Psychiatric disorders (SOC)						
Depression	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Renal and urinary disorders (SOC)						
Renal & urinary tract infection	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	1 (2.0)	0	1 (1.0)
Reproductive system and breast disorders (SOC)						
Abnormal uterine bleeding	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Excessive menstrual bleeding	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Respiratory, thoracic and mediastinal disorders (SOC)						
Respiratory failure	1 (1.8)	0	1.8 (-1.7, 5.3)	0	2 (4.2)	2 (2.0)
Dyspnea	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	1 (2.1)	2 (2.0)
Cough	0	1 (1.8)	-1.8 (-5.3, 1.7)	3 (5.9)	1 (2.1)	4 (4.0)

System Organ Class FMQ (Narrow)	ARGX-113-2001 EFG SC N=55 n (%)	 EFG IV N=55 n (%)	 Risk Difference (%) (95% CI)	ARGX-113-2002 SC-SC (2001) N=51 n (%)	 IV-SC (2001) N=48 n (%)	 Total N=99 n (%)
Skin and subcutaneous tissue disorders (SOC)						
Erythema	7 (12.7)	0	12.7 (3.9, 21.5) *	11 (21.6)	12 (25.0)	23 (23.2)
Rash	9 (16.4)	3 (5.5)	10.9 (-0.6, 22.4)	4 (7.8)	6 (12.5)	10 (10.1)
Pruritus	5 (9.1)	1 (1.8)	7.3 (-1.1, 15.7)	6 (11.8)	5 (10.4)	11 (11.1)
Urticaria	2 (3.6)	0	3.6 (-1.3, 8.6)	2 (3.9)	0	2 (2.0)
Alopecia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Vascular disorders (SOC)						
Hemorrhage	6 (10.9)	5 (9.1)	1.8 (-9.4, 13.0)	11 (21.6)	7 (14.6)	18 (18.2)
Thrombosis	0	1 (1.8)	-1.8 (-5.3, 1.7)	1 (2.0)	0	1 (1.0)
Thrombosis venous	0	1 (1.8)	-1.8 (-5.3, 1.7)	1 (2.0)	0	1 (1.0)

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

The following table shows TEAEs that are grouped together using the FDA Medical Query (Broad). As seen in the table, four TEAEs had risk difference 95% CIs that did not include zero, indicating higher proportions in the EFG PH20 SC group: local administration reaction, hypersensitivity, nasopharyngitis, and erythema

Table 29. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

System Organ Class FMQ (Broad)	ARGX-113-2001 EFG SC N=55 n (%)	 EFG IV N=55 n (%)	 Risk Difference (%) (95% CI)	ARGX-113-2002 SC-SC (2001) N=51 n (%)	 IV-SC (2001) N=48 n (%)	 Total N=99 n (%)
Blood and lymphatic system disorders (SOC)						
Anemia	1 (1.8)	0	1.8 (-1.7, 5.3)	3 (5.9)	2 (4.2)	5 (5.1)
Leukopenia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Thrombocytopenia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Cardiac disorders (SOC)						
Heart failure	4 (7.3)	3 (5.5)	1.8 (-7.3, 10.9)	4 (7.8)	1 (2.1)	5 (5.1)
Systemic hypertension	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	2 (3.9)	1 (2.1)	3 (3.0)
Arrhythmia	2 (3.6)	2 (3.6)	0 (-7.0, 7.0)	3 (5.9)	3 (6.2)	6 (6.1)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	3 (6.2)	3 (3.0)
Tachycardia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	2 (4.2)	2 (2.0)

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Broad)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Ear and labyrinth disorders (SOC)						
Vertigo	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	3 (5.9)	0	3 (3.0)
Endocrine disorders (SOC)						
Hyperglycemia	0	0	0 (0, 0)	3 (5.9)	1 (2.1)	4 (4.0)
Gastrointestinal disorders (SOC)						
Abdominal pain	4 (7.3)	1 (1.8)	5.5 (-2.3, 13.2)	1 (2.0)	1 (2.1)	2 (2.0)
Dyspepsia	5 (9.1)	2 (3.6)	5.5 (-3.6, 14.5)	2 (3.9)	2 (4.2)	4 (4.0)
Dry mouth	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	0	2 (2.0)
Pancreatitis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Diarrhea	1 (1.8)	3 (5.5)	-3.6 (-10.6, 3.3)	7 (13.7)	6 (12.5)	13 (13.1)
Nausea	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	4 (8.3)	5 (5.1)
Vomiting	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	6 (12.5)	7 (7.1)
General disorders and administration site conditions (SOC)						
Local administration reaction	21 (38.2)	3 (5.5)	32.7 (18.6, 46.9) *	23 (45.1)	18 (37.5)	41 (41.4)
Peripheral edema	3 (5.5)	1 (1.8)	3.6 (-3.3, 10.6)	3 (5.9)	0	3 (3.0)
Pyrexia	2 (3.6)	0	3.6 (-1.3, 8.6)	1 (2.0)	3 (6.2)	4 (4.0)
Fatigue	3 (5.5)	3 (5.5)	0 (-8.5, 8.5)	0	5 (10.4)	5 (5.1)
Dizziness	1 (1.8)	2 (3.6)	-1.8 (-7.9, 4.3)	3 (5.9)	0	3 (3.0)
Fall	3 (5.5)	6 (10.9)	-5.5 (-15.6, 4.7)	4 (7.8)	1 (2.1)	5 (5.1)
Hepatobiliary disorders (SOC)						
Cholecystitis	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Hepatic injury	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	0	1 (1.0)
Hepatic failure	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Immune system disorders (SOC)						
Hypersensitivity	10 (18.2)	2 (3.6)	14.5 (3.2, 25.9) *	9 (17.6)	7 (14.6)	16 (16.2)
Angioedema	0	0	0 (0, 0)	2 (3.9)	0	2 (2.0)
Infections and infestations (SOC)						
Nasopharyngitis	4 (7.3)	0	7.3 (0.4, 14.1) *	8 (15.7)	4 (8.3)	12 (12.1)
Fungal infection	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Opportunistic infection	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Viral infection	3 (5.5)	4 (7.3)	-1.8 (-10.9, 7.3)	13 (25.5)	11 (22.9)	24 (24.2)
Bacterial infection	4 (7.3)	6 (10.9)	-3.6 (-14.4, 7.1)	4 (7.8)	3 (6.2)	7 (7.1)
Pneumonia	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	3 (6.2)	4 (4.0)
Metabolism and nutrition disorders (SOC)						
Cachexia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Lipid disorder	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Broad)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Musculoskeletal and connective tissue disorders (SOC)						
Myalgia	2 (3.6)	0	3.6 (-1.3, 8.6)	2 (3.9)	1 (2.1)	3 (3.0)
Arthralgia	1 (1.8)	0	1.8 (-1.7, 5.3)	6 (11.8)	1 (2.1)	7 (7.1)
Arthritis	1 (1.8)	0	1.8 (-1.7, 5.3)	7 (13.7)	1 (2.1)	8 (8.1)
Fracture	1 (1.8)	0	1.8 (-1.7, 5.3)	2 (3.9)	1 (2.1)	3 (3.0)
Back pain	0	0	0 (0, 0)	4 (7.8)	3 (6.2)	7 (7.1)
Osteoporosis	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Tendinopathy	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Nervous system disorders (SOC)						
Dysgeusia	1 (1.8)	0	1.8 (-1.7, 5.3)	1 (2.0)	0	1 (1.0)
Syncope	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	3 (5.9)	0	3 (3.0)
Headache	9 (16.4)	9 (16.4)	0 (-13.8, 13.8)	12 (23.5)	3 (6.2)	15 (15.2)
Paresthesia	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Somnolence	2 (3.6)	3 (5.5)	-1.8 (-9.6, 6.0)	0	4 (8.3)	4 (4.0)
Tremor	0	1 (1.8)	-1.8 (-5.3, 1.7)	1 (2.0)	0	1 (1.0)
Psychiatric disorders (SOC)						
Anxiety	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Depression	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)
Psychosis	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Renal and urinary disorders (SOC)						
Acute kidney injury	0	0	0 (0, 0)	1 (2.0)	0	1 (1.0)
Urinary retention	0	0	0 (0, 0)	2 (3.9)	1 (2.1)	3 (3.0)
Renal & urinary tract infection	2 (3.6)	3 (5.5)	-1.8 (-9.6, 6.0)	1 (2.0)	1 (2.1)	2 (2.0)
Reproductive system and breast disorders (SOC)						
Bacterial vaginosis	1 (1.8)	0	1.8 (-1.7, 5.3)	0	0	0
Abnormal uterine bleeding	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Excessive menstrual bleeding	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Respiratory, thoracic and mediastinal disorders (SOC)						
Respiratory depression	1 (1.8)	0	1.8 (-1.7, 5.3)	0	2 (4.2)	2 (2.0)
Respiratory failure	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	1 (2.0)	2 (4.2)	3 (3.0)
Bronchospasm	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	1 (2.1)	2 (2.0)
Dyspnea	1 (1.8)	1 (1.8)	0 (-5.0, 5.0)	1 (2.0)	1 (2.1)	2 (2.0)
Cough	0	1 (1.8)	-1.8 (-5.3, 1.7)	3 (5.9)	1 (2.1)	4 (4.0)
Skin and subcutaneous tissue disorders (SOC)						
Erythema	7 (12.7)	0	12.7 (3.9, 21.5) *	11 (21.6)	12 (25.0)	23 (23.2)
Rash	9 (16.4)	3 (5.5)	10.9 (-0.6, 22.4)	5 (9.8)	7 (14.6)	12 (12.1)
Pruritus	5 (9.1)	1 (1.8)	7.3 (-1.1, 15.7)	6 (11.8)	5 (10.4)	11 (11.1)
Urticaria	2 (3.6)	1 (1.8)	1.8 (-4.3, 7.9)	2 (3.9)	0	2 (2.0)
Alopecia	0	0	0 (0, 0)	0	1 (2.1)	1 (1.0)

System Organ Class FMQ (Broad)	ARGX-113-2001 EFG SC N=55 n (%)	 EFG IV N=55 n (%)	 Risk Difference (%) (95% CI)	ARGX-113-2002 SC-SC (2001) N=51 n (%)	 IV-SC (2001) N=48 n (%)	 Total N=99 n (%)
Vascular disorders (SOC)						
Hemorrhage	6 (10.9)	5 (9.1)	1.8 (-9.4, 13.0)	11 (21.6)	7 (14.6)	18 (18.2)
Thrombosis	0	1 (1.8)	-1.8 (-5.3, 1.7)	1 (2.0)	0	1 (1.0)
Thrombosis venous	0	1 (1.8)	-1.8 (-5.3, 1.7)	1 (2.0)	0	1 (1.0)

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Broad) and Preferred Term…"
Abbreviations: AE, adverse event; CI, confidence interval; EFG, efgartigimod; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

The 90-day safety update reported that five additional PTs reached the threshold for common AEs in Study 2002 (i.e., ≥5% of subjects): anemia (12 of 177, 7%), upper respiratory tract infection (11 of 177, 6%), back pain (10 of 177, 6%), myasthenia gravis (10 of 177, 6%), nausea (9 of 177, 5%).

7.6.1.6. Laboratory Findings, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of laboratory value abnormalities for Studies 2001 and the subjects who then continued into Study 2002 are shown in the following tables. Overall, there were no clinically significant patterns or trends observed in abnormalities in blood chemistry differentiating EFG PH20 SC from EFG IV.

Table 30. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

Laboratory Parameter	ARGX-113-2001 EFG SC N=55 n/N_w (%)	 EFG IV N=55 n/N_w (%)	 Risk Difference (%) (95% CI)	ARGX-113-2002 SC-SC (2001) N=51 n/N_w (%)	 IV-SC (2001) N=48 n/N_w (%)	 Total N=99 n/N_w (%)
Sodium, low (mEq/L)						
Level 1 (<132)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	1/48 (2.1)	1/99 (1.0)
Level 2 (<130)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (<125)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Sodium, high (mEq/L)						
Level 1 (>150)	0/55 (0)	1/55 (1.8)	-1.8 (-5.3, 1.7)	0/51 (0)	0/48 (0)	0/99 (0)
Level 2 (>155)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (>160)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Potassium, low (mEq/L)						
Level 1 (<3.6)	10/55 (18.2)	12/55 (21.8)	-3.6 (-18.6, 11.3)	8/51 (15.7)	7/48 (14.6)	15/99 (15.2)
Level 2 (<3.4)	5/55 (9.1)	5/55 (9.1)	0 (-10.7, 10.7)	3/51 (5.9)	2/48 (4.2)	5/99 (5.1)
Level 3 (<3)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)

	ARGX-113-2001			ARGX-113-2002		
Laboratory Parameter	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
Potassium, high (mEq/L)						
Level 1 (>5.5)	1/55 (1.8)	1/55 (1.8)	0 (-5.0, 5.0)	0/51 (0)	1/48 (2.1)	1/99 (1.0)
Level 2 (>6)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	1/48 (2.1)	1/99 (1.0)
Level 3 (>6.5)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Chloride, low (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA
Chloride, high (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA
Bicarbonate, low (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA
Bicarbonate, high (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA
Glucose, low (mg/dL)						
Level 1 (<70)	7/55 (12.7)	8/55 (14.5)	-1.8 (-14.6, 11.0)	4/51 (7.8)	3/48 (6.2)	7/99 (7.1)
Level 2 (<54)	1/55 (1.8)	3/55 (5.5)	-3.6 (-10.6, 3.3)	0/51 (0)	1/48 (2.1)	1/99 (1.0)
Level 3 (<40)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Glucose, fasting, high (mg/dL)						
Level 1 (≥100 to 125)	17/55 (30.9)	16/55 (29.1)	1.8 (-15.3, 18.9)	17/51 (33.3)	18/48 (37.5)	35/99 (35.4)
Level 2 (≥126)	13/55 (23.6)	13/55 (23.6)	0 (-15.9, 15.9)	12/51 (23.5)	9/48 (18.8)	21/99 (21.2)
Glucose, random, high (mg/dL)						
Level 2 (≥200)	1/4 (25.0)	0/5 (0)	25.0 (-17.4, 67.4)	1/7 (14.3)	1/7 (14.3)	2/14 (14.3)
Level 3 (>250)	0/4 (0)	0/5 (0)	0 (0, 0)	1/7 (14.3)	1/7 (14.3)	2/14 (14.3)
Calcium, low (mg/dL)						
Level 1 (<8.4)	1/55 (1.8)	1/55 (1.8)	0 (-5.0, 5.0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 2 (<8)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (<7.5)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Calcium, high (mg/dL)						
Level 1 (>10.5)	5/55 (9.1)	3/55 (5.5)	3.6 (-6.0, 13.3)	6/51 (11.8)	10/48 (20.8)	16/99 (16.2)
Level 2 (>11)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	1/51 (2.0)	1/48 (2.1)	2/99 (2.0)
Level 3 (>12)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Magnesium, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)						
Missing	NA	NA	NA	NA	NA	NA
Albumin, low (g/dL)						
Level 1 (<3.1)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 2 (<2.5)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (<2)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)

	ARGX-113-2001			ARGX-113-2002		
Laboratory Parameter	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
CPK, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Amylase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	13/55 (23.6)	8/55 (14.5)	9.1 (-5.5, 23.7)	7/51 (13.7)	12/48 (25.0)	19/99 (19.2)
Level 2 (>27)	4/55 (7.3)	4/55 (7.3)	0 (-9.7, 9.7)	4/51 (7.8)	5/48 (10.4)	9/99 (9.1)
Level 3 (>31)	1/55 (1.8)	3/55 (5.5)	-3.6 (-10.6, 3.3)	2/51 (3.9)	3/48 (6.2)	5/99 (5.1)

Source: adlb.xpt; Software: R
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; NA, not applicable; SC, subcutaneous

There was no clinically significant difference observed in hematological parameters between the EFG PH20 SC group and the EFG IV group, as seen in the following table.

Table 31. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Laboratory Parameter	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
Complete Blood Count						
WBC, low (cells/uL)						
Level 1 (<3500)	5/55 (9.1)	4/55 (7.3)	1.8 (-8.4, 12.1)	7/51 (13.7)	3/48 (6.2)	10/99 (10.1)
Level 2 (<3000)	1/55 (1.8)	1/55 (1.8)	0 (-5.0, 5.0)	1/51 (2.0)	2/48 (4.2)	3/99 (3.0)
Level 3 (<1000)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
WBC, high (cells/uL)						
Level 1 (>10800)	14/55 (25.5)	18/55 (32.7)	-7.3 (-24.2, 9.6)	11/51 (21.6)	16/48 (33.3)	27/99 (27.3)
Level 2 (>13000)	6/55 (10.9)	10/55 (18.2)	-7.3 (-20.4, 5.8)	3/51 (5.9)	8/48 (16.7)	11/99 (11.1)
Level 3 (>15000)	2/55 (3.6)	4/55 (7.3)	-3.6 (-12.1, 4.8)	2/51 (3.9)	5/48 (10.4)	7/99 (7.1)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 g/dL dec. from baseline)	12/55 (21.8)	13/55 (23.6)	-1.8 (-17.5, 13.8)	6/49 (12.2)	3/47 (6.4)	9/96 (9.4)
Level 3 (>2 g/dL dec. from baseline)	4/55 (7.3)	3/55 (5.5)	1.8 (-7.3, 10.9)	2/49 (4.1)	1/47 (2.1)	3/96 (3.1)

	ARGX-113-2001			ARGX-113-2002		
Laboratory Parameter	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
Hemoglobin, high (g/dL)						
Level 2 (>2 g/dL inc. from baseline)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	2/49 (4.1)	1/47 (2.1)	3/96 (3.1)
Level 3 (>3 g/dL inc. from baseline)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	0/49 (0)	1/47 (2.1)	1/96 (1.0)
Platelets, low (cells/uL)						
Level 1 (<140000)	3/55 (5.5)	1/55 (1.8)	3.6 (-3.3, 10.6)	3/51 (5.9)	3/48 (6.2)	6/99 (6.1)
Level 2 (<125000)	2/55 (3.6)	1/55 (1.8)	1.8 (-4.3, 7.9)	1/51 (2.0)	1/48 (2.1)	2/99 (2.0)
Level 3 (<100000)	0/55 (0)	0/55 (0)	0 (0, 0)	1/51 (2.0)	0/48 (0)	1/99 (1.0)
WBC Differential						
Lymphocytes, low (cells/uL)						
Level 1 (<1000)	19/55 (34.5)	23/55 (41.8)	-7.3 (-25.4, 10.8)	17/51 (33.3)	20/48 (41.7)	37/99 (37.4)
Level 2 (<750)	12/55 (21.8)	11/55 (20.0)	1.8 (-13.4, 17.0)	9/51 (17.6)	12/48 (25.0)	21/99 (21.2)
Level 3 (<500)	4/55 (7.3)	3/55 (5.5)	1.8 (-7.3, 10.9)	5/51 (9.8)	2/48 (4.2)	7/99 (7.1)
Lymphocytes, high (cells/uL)						
Level 1 (>4000)	3/55 (5.5)	5/55 (9.1)	-3.6 (-13.3, 6.0)	2/51 (3.9)	2/48 (4.2)	4/99 (4.0)
Level 2 (>10000)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (>20000)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Neutrophils, low (cells/uL)						
Level 1 (<2000)	6/55 (10.9)	4/55 (7.3)	3.6 (-7.1, 14.4)	12/51 (23.5)	2/48 (4.2)	14/99 (14.1)
Level 2 (<1000)	0/55 (0)	1/55 (1.8)	-1.8 (-5.3, 1.7)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (<500)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Eosinophils, high (cells/uL)						
Level 1 (>650)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	1/51 (2.0)	0/48 (0)	1/99 (1.0)
Level 2 (>1500)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	1/51 (2.0)	0/48 (0)	1/99 (1.0)
Level 3 (>5000)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Coagulation Studies						
PT, high (sec)						
Level 1 (>1.1X ULN)	5/55 (9.1)	8/55 (14.5)	-5.5 (-17.5, 6.6)	1/51 (2.0)	6/48 (12.5)	7/99 (7.1)
Level 2 (>1.3X ULN)	3/55 (5.5)	4/55 (7.3)	-1.8 (-10.9, 7.3)	1/51 (2.0)	3/48 (6.2)	4/99 (4.0)
Level 3 (>1.5X ULN)	1/55 (1.8)	1/55 (1.8)	0 (-5.0, 5.0)	1/51 (2.0)	0/48 (0)	1/99 (1.0)
PTT, high (sec)						
Level 1 (>1X ULN)	16/55 (29.1)	21/55 (38.2)	-9.1 (-26.7, 8.5)	9/51 (17.6)	18/48 (37.5)	27/99 (27.3)
Level 2 (>1.21X ULN)	4/55 (7.3)	5/55 (9.1)	-1.8 (-12.1, 8.4)	2/51 (3.9)	7/48 (14.6)	9/99 (9.1)
Level 3 (>1.41X ULN)	1/55 (1.8)	2/55 (3.6)	-1.8 (-7.9, 4.3)	0/51 (0)	4/48 (8.3)	4/99 (4.0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; SC, subcutaneous; ULN, upper limit of normal; WBC, White blood cells

7.6.1.7. Assessment of Drug-Induced Liver Injury, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

Results of the FDA analysis of liver lab abnormalities for Studies 2001 and the subjects who then continued into Study 2002 are shown in the following tables. There were no clinically significant patterns or trends observed in abnormalities in liver chemistry differing between the EFG PH20 SC group and the EFG IV group.

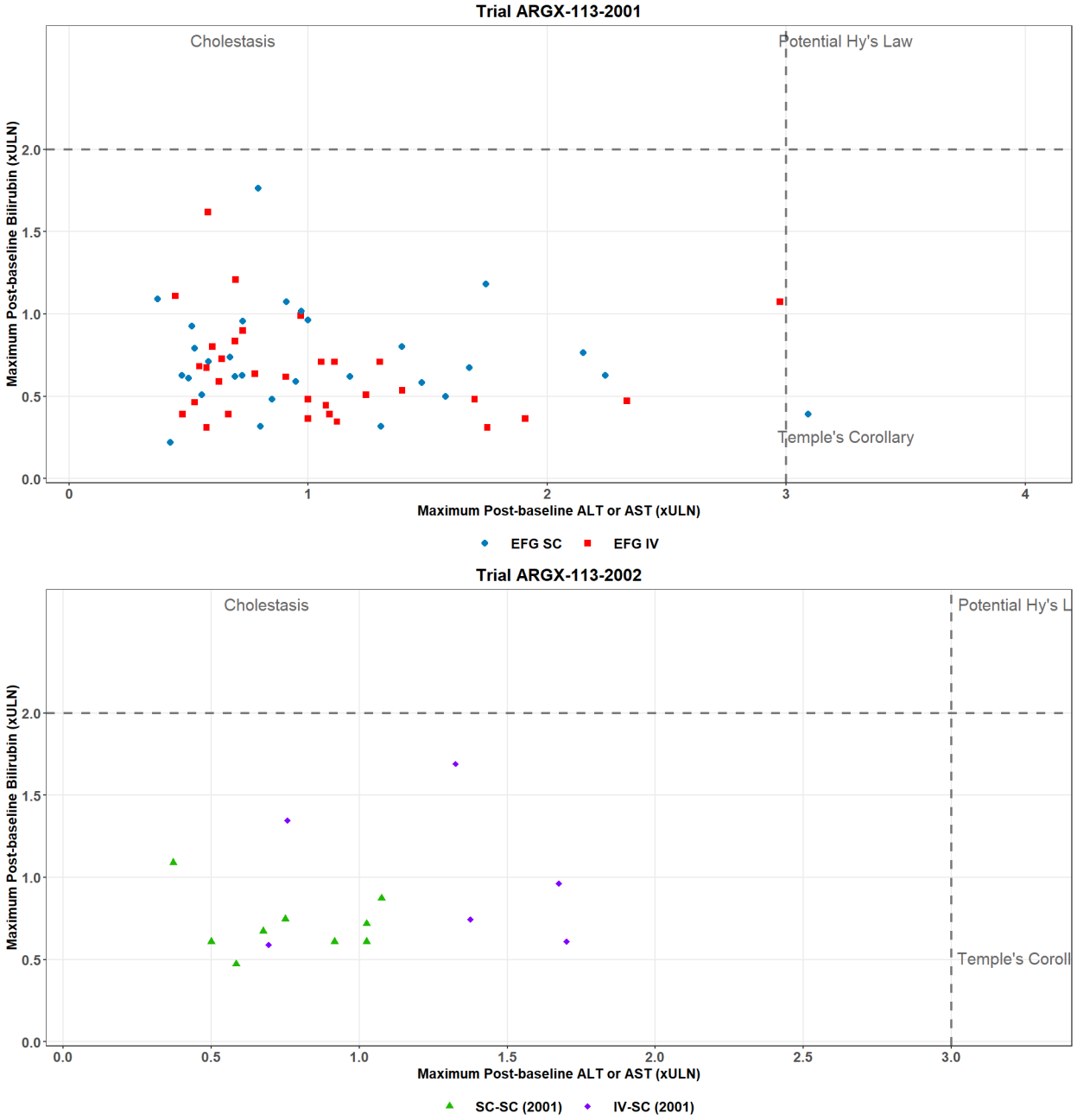
Table 32: Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Laboratory Parameter	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	2/55 (3.6)	2/55 (3.6)	0 (-7.0, 7.0)	2/51 (3.9)	1/48 (2.1)	3/99 (3.0)
Level 2 (>2X ULN)	1/55 (1.8)	1/55 (1.8)	0 (-5.0, 5.0)	1/51 (2.0)	1/48 (2.1)	2/99 (2.0)
Level 3 (>3X ULN)	0/55 (0)	1/55 (1.8)	-1.8 (-5.3, 1.7)	0/51 (0)	1/48 (2.1)	1/99 (1.0)
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	1/51 (2.0)	1/48 (2.1)	2/99 (2.0)
Level 2 (>5X ULN)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (>10X ULN)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	0/51 (0)	0/48 (0)	0/99 (0)
Level 2 (>5X ULN)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (>10X ULN)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	3/55 (5.5)	3/55 (5.5)	0 (-8.5, 8.5)	0/51 (0)	2/48 (4.2)	2/99 (2.0)
Level 2 (>2X ULN)	1/55 (1.8)	0/55 (0)	1.8 (-1.7, 5.3)	0/51 (0)	0/48 (0)	0/99 (0)
Level 3 (>3X ULN)	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/48 (0)	0/99 (0)

Source: adlb.xpt; Software: R
Duration is 3 weeks for Study ARGX-113-2001 and 2 years for Study ARGX-113-2002.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Subjects in Each Quadrant for Cholestatic DILI Screening Plot…"
Abbreviations: CI, confidence interval; DILI, drug-induced liver injury; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous; ULN, upper limit of normal

The following figure and table show a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no Hy's law cases.

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EFG, efgartigimod; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal

Table 33. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001		ARGX-113-2002		
Quadrant	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
Potential Hy's Law (right upper)	0/55 (0)	0/55 (0)	0/51 (0)	0/48 (0)	0/99 (0)
Cholestasis (left upper)	0/55 (0)	0/55 (0)	0/51 (0)	0/48 (0)	0/99 (0)
Temple's corollary (right lower)	1/55 (1.8)	0/55 (0)	0/51 (0)	0/48 (0)	0/99 (0)
Total	1/55 (1.8)	0/55 (0)	0/51 (0)	0/48 (0)	0/99 (0)

Source: adlb.xpt; Software: R
Abbreviations: DILI, drug-induced liver injury; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous

7.6.1.8. Vital Signs, Pooled Analyses, Studies 2001 and 2002 (Subjects Rolled Over From Study 2001 Only)

There were no clinically significant patterns or trends observed in abnormalities in vital signs (including diastolic and systolic blood pressure, pulse rate, and temperature) differing between the EFG PH20 SC group and the EFG IV group in Study 2001 and the subjects who then continued into Study 2002. Respiratory rate data were not included in vital signs datasets.

Table 34. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Systolic Blood Pressure (mm Hg)	EFG SC N=55 n/Nw (%)	EFG IV N=55 n/Nw (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/Nw (%)	IV-SC (2001) N=48 n/Nw (%)	Total N=99 n/Nw (%)
<90	0/55 (0)	0/55 (0)	0 (0, 0)	0/51 (0)	0/47 (0)	0/98 (0)
≥90	55/55 (100)	55/55 (100)	0 (0, 0)	51/51 (100)	47/47 (100)	98/98 (100)
≥120	48/55 (87.3)	49/55 (89.1)	-1.8 (-13.9, 10.2)	44/51 (86.3)	40/47 (85.1)	84/98 (85.7)
≥140	24/55 (43.6)	25/55 (45.5)	-1.8 (-20.4, 16.8)	17/51 (33.3)	18/47 (38.3)	35/98 (35.7)
≥160	3/55 (5.5)	5/55 (9.1)	-3.6 (-13.3, 6.0)	6/51 (11.8)	0/47 (0)	6/98 (6.1)
≥180	0/55 (0)	1/55 (1.8)	-1.8 (-5.3, 1.7)	1/51 (2.0)	0/47 (0)	1/98 (1.0)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.\
Abbreviations: CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous

Table 35. Percentage of Subjects With Meeting Specific Hypotension Levels Post-Baseline, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Blood Pressure (mm Hg)	EFG SC N=55 n/N_w (%)	EFG IV N=55 n/N_w (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_w (%)	IV-SC (2001) N=48 n/N_w (%)	Total N=99 n/N_w (%)
SBP <90	3/55 (5.5)	2/55 (3.6)	1.8 (-6.0, 9.6)	3/51 (5.9)	0/47 (0)	3/98 (3.1)
DBP <60	5/55 (9.1)	4/55 (7.3)	1.8 (-8.4, 12.1)	2/51 (3.9)	3/47 (6.4)	5/98 (5.1)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SBP, systolic blood pressure; SC, subcutaneous)

Results of the FDA analysis of SAEs and AEs by demographic subgroup for the EFG PH20 SC group and the EFG IV group in Study 2001 and the subjects who then continued into Study 2002 are shown in the following tables.

Table 36. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Characteristic	EFG SC N=55 n/N_s (%)	EFG IV N=55 n/N_s (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_s (%)	IV-SC (2001) N=48 n/N_s (%)	Total N=99 n/N_s (%)
Sex, n (%)						
Female	8/31 (25.8)	3/34 (8.8)	17.0 (-1.1, 35.1)	7/28 (25.0)	3/30 (10.0)	10/58 (17.2)
Male	6/24 (25.0)	5/21 (23.8)	1.2 (-23.9, 26.3)	6/23 (26.1)	4/18 (22.2)	10/41 (24.4)
Age group, years, n (%)						
≥65 years	4/12 (33.3)	3/18 (16.7)	16.7 (-15.1, 48.4)	4/12 (33.3)	3/15 (20.0)	7/27 (25.9)
18 to 64 years	10/43 (23.3)	5/37 (13.5)	9.7 (-7.0, 26.5)	9/39 (23.1)	4/33 (12.1)	13/72 (18.1)
Age group ≥75, years, n (%)						
≥75	0/2 (0)	1/5 (20.0)	-20.0 (-55.1, 15.1)	0/2 (0)	1/5 (20.0)	1/7 (14.3)
Race, n (%)						
Asian	1/4 (25.0)	0/4 (0)	25.0 (-17.4, 67.4)	1/4 (25.0)	0/3 (0)	1/7 (14.3)
Multiple	1/1 (100)	0/0 (NA)	NA	1/1 (100)	0/0 (NA)	1/1 (100)
White	12/50 (24.0)	8/51 (15.7)	8.3 (-7.2, 23.8)	11/46 (23.9)	7/45 (15.6)	18/91 (19.8)
Ethnicity, n (%)						
Hispanic or Latino	1/3 (33.3)	1/2 (50.0)	-16.7 (-104.1, 70.8)	1/3 (33.3)	1/2 (50.0)	2/5 (40.0)
Not Hispanic or Latino	13/52 (25.0)	7/53 (13.2)	11.8 (-3.1, 26.7)	12/48 (25.0)	6/46 (13.0)	18/94 (19.1)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; SC, subcutaneous

Table 37. Overview of Adverse Events by Demographic Subgroup, Safety Population, Studies ARGX-113-2001 and ARGX-113-2002

	ARGX-113-2001			ARGX-113-2002		
Characteristic	EFG SC N=55 n/N_s (%)	EFG IV N=55 n/N_s (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n/N_s (%)	IV-SC (2001) N=48 n/N_s (%)	Total N=99 n/N_s (%)
Sex, n (%)						
Female	31/31 (100)	28/34 (82.4)	17.6 (4.8, 30.5) *	28/28 (100)	25/30 (83.3)	53/58 (91.4)
Male	17/24 (70.8)	12/21 (57.1)	13.7 (-14.2, 41.6)	17/23 (73.9)	11/18 (61.1)	28/41 (68.3)
Age group, years, n (%)						
≥65 years	10/12 (83.3)	13/18 (72.2)	11.1 (-18.4, 40.7)	10/12 (83.3)	11/15 (73.3)	21/27 (77.8)
18 to 64 years	38/43 (88.4)	27/37 (73.0)	15.4 (-1.8, 32.6)	35/39 (89.7)	25/33 (75.8)	60/72 (83.3)
Age group ≥75, years, n (%)						
≥75	1/2 (50.0)	4/5 (80.0)	-30.0 (-107.7, 47.7)	1/2 (50.0)	4/5 (80.0)	5/7 (71.4)
Race, n (%)						
Asian	3/4 (75.0)	3/4 (75.0)	0 (-60.0, 60.0)	3/4 (75.0)	3/3 (100)	6/7 (85.7)
Multiple	1/1 (100)	0/0 (NA)	NA	1/1 (100)	0/0 (NA)	1/1 (100)
White	44/50 (88.0)	37/51 (72.5)	15.5 (0.2, 30.7) *	41/46 (89.1)	33/45 (73.3)	74/91 (81.3)
Ethnicity, n (%)						
Hispanic or Latino	3/3 (100)	2/2 (100)	0 (0, 0)	3/3 (100)	2/2 (100)	5/5 (100)
Not Hispanic or Latino	45/52 (86.5)	38/53 (71.7)	14.8 (-0.4, 30.1)	42/48 (87.5)	34/46 (73.9)	76/94 (80.9)

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between EFG SC and EFG IV.
Abbreviations: CI, confidence interval; EFG, efgartigimod; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; SC, subcutaneous

Overall, there appears to be a trend of more SAEs and AEs in the EFG PH20 SC than in the EFG IV group across demographic subgroups. There were no clinically significant differences in the proportions of subjects with AEs or SAEs as a function of age or sex subgroup. There was also no clinically significant difference in the proportion of subjects with AEs as a function of race or ethnicity, although the small numbers of subjects in these subgroups make the result difficult to interpret.

7.6.2. Safety Results, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of adverse events for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following table.

Table 38. Overview of Adverse Events, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Event Category	IV-SC (1705) N=65 n (%)
SAE	4 (6.2)
SAEs with fatal outcome	1 (1.5)
Life-threatening SAEs	1 (1.5)
AE leading to permanent discontinuation of study drug	2 (3.1)
AE leading to dose modification of study drug	3 (4.6)
AE leading to interruption of study drug	2 (3.1)
AE leading to reduction of study drug	1 (1.5)
AE leading to dose delay of study drug	0
Other	0
Any AE	49 (75.4)
Severe and worse	6 (9.2)
Moderate	23 (35.4)
Mild	20 (30.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 2 years.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous

Overall, there is a lower proportion of SAEs (6%) and a similar proportion of AEs (75%) compared to those for subjects rolled over from Study 2001 (SAEs 13%, AEs 77%; see Section 7.6.1.1) and for the safety population in the original efgartigimod IV BLA 761195 (SAEs 14%, AEs 83%), as seen in the following table copied from the clinical review of BLA 761195.

Table 39. Overview of Treatment-Emergent Adverse Events, All Efgartigimod-Treated Study Safety Population From BLA 761195, Vyvgart (Efgartigimod Alfa - fcab)

Event	Efgartigimod (N=162) n (%)
Any treatment-emergent AE[1]	134 (83)
Moderate or severe AEs (Grade 3-5)[2]	31 (19)
SAEs	23 (14)
SAEs with fatal outcome	5 (3)
AEs leading to trial discontinuation	5 (3)
AEs leading to discontinuation of trial drug	11 (7)

Source: Clinical Safety Reviewer
[1] Includes treatment-emergent AE defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] CTCAE grading scale used for toxicity grades
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

Source: Table 38 of Clinical Review for BLA 761195

7.6.2.2. Deaths, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

One 83-year-old female subject (1.5%), who had previously received efgartigimod IV in the open-label extension Study 1705 from the original efgartigimod BLA 761195 and then switched to efgartigimod/rHuPH20 SC in Study 2002, died due to AEs of COVID-19 and respiratory failure. This subject had a medical history of hypertension, heart failure, ischemic heart disease, and type 2 diabetes that likely increased the risk of death from COVID-19.

Table 40. Deaths, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Preferred Term	IV-SC (1705) N=65 n (%)
Any AE leading to death	1 (1.5)
COVID-19	1 (1.5)
Respiratory failure	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 2 years.
For patient-level data, see the table "List of Adverse Events Leading to Death
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of serious adverse events for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following table.

Overall, there is a lower proportion of SAEs (6%) than for subjects rolled over from Study 2001 (SAEs 13%; see Section 7.6.1.1) and the safety population in the original efgartigimod IV BLA 761195 (SAEs 14%).

Table 41. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class Preferred Term	IV-SC (1705) N=65 n (%)
Any SAE	4 (6.2)
Infections and infestations (SOC)	1 (1.5)
COVID-19	1 (1.5)
Musculoskeletal and connective tissue disorders (SOC)	1 (1.5)
Back pain	1 (1.5)
Nervous system disorders (SOC)	2 (3.1)
Myasthenia gravis	1 (1.5)
Myasthenia gravis crisis	1 (1.5)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.5)
Respiratory failure	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 2 years.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class

Table 42. Subjects With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class FMQ (Narrow)	IV-SC (1705) N=65 n (%)
Infections and infestations (SOC)	
Viral infection	1 (1.5)
Musculoskeletal and connective tissue disorders (SOC)	
Back pain	1 (1.5)
Respiratory, thoracic, and mediastinal disorders (SOC)	
Respiratory failure	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 2 years.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. For specific preferred terms under each FMQ, see the table “Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: AE, adverse event; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of adverse events leading to treatment discontinuation for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following table.

In Study 2002, two subjects (3%) from Study 1705 (COVID-19/respiratory failure and myasthenia gravis) and one subject from Study 2001 (renal cancer metastatic) had AEs leading to treatment discontinuation.

Table 43. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class Preferred Term	IV-SC (1705) N=65 n (%)
Any AE leading to Discontinuation	2 (3.1)
Infections and infestations (SOC)	1 (1.5)
COVID-19	1 (1.5)
Nervous system disorders (SOC)	1 (1.5)
Myasthenia gravis crisis	1 (1.5)
Respiratory, thoracic, and mediastinal disorders (SOC)	1 (1.5)
Respiratory failure	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod. Duration is 2 years.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous; SOC, system organ class

Table 44. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class FMQ (Narrow)	IV-SC (1705) N=65 n (%)
Infections and infestations (SOC)	
Viral infection	1 (1.5)
Respiratory, thoracic and mediastinal disorders (SOC)	
Respiratory failure	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod. Duration is 2 years.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of TEAEs for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following tables if there were at least two subjects with adverse events by PT, FDA Medical Query (Narrow), and FDA Medical Query (Broad). The proportion of subjects experiencing TEAEs was similar (75%) in subjects rolled over from Study 1705 compared to subjects rolled over from Study 2001 (77%, see Section 7.6.1.5). Injection site reactions are further discussed in Section 7.7.3.

Table 45. Subjects With Common Adverse Events Occurring at ≥3% Frequency, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Preferred Term	IV-SC (1705) N=65 n (%)
Any AE	49 (75.4)
Injection site erythema	19 (29.2)
Headache	11 (16.9)
COVID-19	8 (12.3)
Injection site pain	8 (12.3)
Injection site pruritus	7 (10.8)
Injection site bruising	6 (9.2)
Injection site swelling	6 (9.2)
Nasopharyngitis	5 (7.7)
Diarrhoea	3 (4.6)
Injection site oedema	3 (4.6)
Muscle spasms	3 (4.6)
Pruritus	3 (4.6)
Abdominal pain upper	2 (3.1)
Anemia	2 (3.1)
Arthralgia	2 (3.1)
Back pain	2 (3.1)
Dry skin	2 (3.1)
Injection site rash	2 (3.1)
Migraine	2 (3.1)
Myasthenia gravis	2 (3.1)
Nausea	2 (3.1)
Nephrolithiasis	2 (3.1)
Pain in extremity	2 (3.1)
Proteinuria	2 (3.1)
Rash macular	2 (3.1)
Sinusitis	2 (3.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod.
Duration is 2 years.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

The following table shows TEAEs that are grouped together using the FDA Medical Query (Narrow). Local administration reactions (43%) and erythema (29%) had the highest frequency and were similar to the rates seen in subjects rolled over from Study 2001 (41% and 23%, respectively; see Section 7.6.1.5).

Table 46. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class FMQ (Narrow)	IV-SC (1705) N=65 n (%)
Blood and lymphatic system disorders (SOC)	
Anemia	2 (3.1)
Cardiac disorders (SOC)	
Arrhythmia	1 (1.5)
Systemic hypertension	1 (1.5)
Tachycardia	1 (1.5)

System Organ Class FMQ (Narrow)	IV-SC (1705) N=65 n (%)
Ear and labyrinth disorders (SOC)	
Vertigo	1 (1.5)
Endocrine disorders (SOC)	
Hyperglycemia	2 (3.1)
Gastrointestinal disorders (SOC)	
Abdominal pain	3 (4.6)
Diarrhea	3 (4.6)
Dyspepsia	2 (3.1)
Nausea	2 (3.1)
Constipation	1 (1.5)
Dry mouth	1 (1.5)
Vomiting	1 (1.5)
General disorders and administration site conditions (SOC)	
Local administration reaction	28 (43.1)
Dizziness	1 (1.5)
Fatigue	1 (1.5)
Pyrexia	1 (1.5)
Infections and infestations (SOC)	
Viral infection	9 (13.8)
Nasopharyngitis	6 (9.2)
Bacterial infection	1 (1.5)
Fungal infection	1 (1.5)
Metabolism and nutrition disorders (SOC)	
Lipid disorder	1 (1.5)
Musculoskeletal and connective tissue disorders (SOC)	
Arthralgia	2 (3.1)
Back pain	2 (3.1)
Nervous system disorders (SOC)	
Headache	11 (16.9)
Paresthesia	1 (1.5)
Renal and urinary disorders (SOC)	
Renal & urinary tract infection	1 (1.5)
Respiratory, thoracic and mediastinal disorders (SOC)	
Dyspnea	1 (1.5)
Respiratory failure	1 (1.5)

System Organ Class FMQ (Narrow)	IV-SC (1705) N=65 n (%)
Skin and subcutaneous tissue disorders (SOC)	
Erythema	19 (29.2)
Pruritus	9 (13.8)
Rash	6 (9.2)
Vascular disorders (SOC)	
Hemorrhage	7 (10.8)
Thrombosis	1 (1.5)
Thrombosis venous	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod. Duration is 2 years.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: AE, adverse event; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

The following table shows TEAEs that are grouped together using the FDA Medical Query (Broad). Local administration reactions (43%) and erythema (29%) had the highest frequency and were similar to the rates seen in subjects rolled over from Study 2001 (41% and 23%, respectively; see Section 7.6.1.5).

Table 47. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

System Organ Class FMQ (Broad)	IV-SC (1705) N=65 n (%)
Blood and lymphatic system disorders (SOC)	
Anemia	2 (3.1)
Leukopenia	1 (1.5)
Cardiac disorders (SOC)	
Arrhythmia	2 (3.1)
Heart failure	1 (1.5)
Systemic hypertension	1 (1.5)
Tachycardia	1 (1.5)
Ear and labyrinth disorders (SOC)	
Vertigo	1 (1.5)
Endocrine disorders (SOC)	
Hyperglycemia	2 (3.1)
Gastrointestinal disorders (SOC)	
Diarrhea	4 (6.2)
Abdominal pain	3 (4.6)
Nausea	3 (4.6)
Vomiting	3 (4.6)
Dyspepsia	2 (3.1)
Constipation	1 (1.5)
Dry mouth	1 (1.5)

System Organ Class FMQ (Broad)	IV-SC (1705) N=65 n (%)
General disorders and administration site conditions (SOC)	
Local administration reaction	28 (43.1)
Dizziness	1 (1.5)
Fall	1 (1.5)
Fatigue	1 (1.5)
Pyrexia	1 (1.5)
Hepatobiliary disorders (SOC)	
Hepatic injury	1 (1.5)
Immune system disorders (SOC)	
Hypersensitivity	9 (13.8)
Anaphylactic reaction	1 (1.5)
Angioedema	1 (1.5)
Infections and infestations (SOC)	
Viral infection	9 (13.8)
Nasopharyngitis	6 (9.2)
Bacterial infection	4 (6.2)
Fungal infection	1 (1.5)
Metabolism and nutrition disorders (SOC)	
Lipid disorder	1 (1.5)
Musculoskeletal and connective tissue disorders (SOC)	
Arthralgia	3 (4.6)
Arthritis	3 (4.6)
Myalgia	3 (4.6)
Back pain	2 (3.1)
Nervous system disorders (SOC)	
Headache	11 (16.9)
Paresthesia	1 (1.5)
Somnolence	1 (1.5)
Renal and urinary disorders (SOC)	
Renal & urinary tract infection	1 (1.5)
Reproductive system and breast disorders (SOC)	
Sexual dysfunction	1 (1.5)
Respiratory, thoracic and mediastinal disorders (SOC)	
Respiratory failure	2 (3.1)
Bronchospasm	1 (1.5)
Dyspnea	1 (1.5)
Respiratory depression	1 (1.5)
Skin and subcutaneous tissue disorders (SOC)	
Erythema	19 (29.2)
Pruritus	9 (13.8)
Rash	6 (9.2)
Urticaria	1 (1.5)

System Organ Class FMQ (Broad)	IV-SC (1705) N=65 n (%)
Vascular disorders (SOC)	
Hemorrhage	7 (10.8)
Thrombosis	1 (1.5)
Thrombosis venous	1 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started during or after the first administration of efgartigimod. Duration is 2 years.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Broad) and Preferred Term…"
Abbreviations: AE, adverse event; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SC, subcutaneous; SOC, system organ class

7.6.2.6. Laboratory Findings, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of laboratory value abnormalities for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following tables. Overall, there were no clinically significant patterns or trends observed in abnormalities in blood chemistry.

Table 48. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Laboratory Parameter	IV-SC (1705) N=65 n/N_w (%)
Sodium, low (mEq/L)	
Level 1 (<132)	0/65 (0)
Level 2 (<130)	0/65 (0)
Level 3 (<125)	0/65 (0)
Sodium, high (mEq/L)	
Level 1 (>150)	0/65 (0)
Level 2 (>155)	0/65 (0)
Level 3 (>160)	0/65 (0)
Potassium, low (mEq/L)	
Level 1 (<3.6)	5/65 (7.7)
Level 2 (<3.4)	0/65 (0)
Level 3 (<3)	0/65 (0)
Potassium, high (mEq/L)	
Level 1 (>5.5)	0/65 (0)
Level 2 (>6)	0/65 (0)
Level 3 (>6.5)	0/65 (0)
Chloride, low (mEq/L)	
Missing	NA
Chloride, high (mEq/L)	
Missing	NA
Bicarbonate, low (mEq/L)	
Missing	NA
Bicarbonate, high (mEq/L)	
Missing	NA

Laboratory Parameter	IV-SC (1705) N=65 n/N_w (%)
Glucose, low (mg/dL)	
Level 1 (<70)	5/65 (7.7)
Level 2 (<54)	0/65 (0)
Level 3 (<40)	0/65 (0)
Glucose, fasting, high (mg/dL)	
Level 1 (≥100 to 125)	28/65 (43.1)
Level 2 (≥126)	7/65 (10.8)
Glucose, random, high (mg/dL)	
Level 2 (≥200)	0/6 (0)
Level 3 (>250)	0/6 (0)
Calcium, low (mg/dL)	
Level 1 (<8.4)	0/65 (0)
Level 2 (<8)	0/65 (0)
Level 3 (<7.5)	0/65 (0)
Calcium, high (mg/dL)	
Level 1 (>10.5)	2/65 (3.1)
Level 2 (>11)	1/65 (1.5)
Level 3 (>12)	0/65 (0)
Magnesium, low (mg/dL)	
Missing	NA
Magnesium, high (mg/dL)	
Missing	NA
Phosphate, low (mg/dL)	
Missing	NA
Protein, total, low (g/dL)	
Missing	NA
Albumin, low (g/dL)	
Level 1 (<3.1)	0/65 (0)
Level 2 (<2.5)	0/65 (0)
Level 3 (<2)	0/65 (0)
CPK, high (U/L)	
Missing	NA
Amylase, high (U/L)	
Missing	NA
Lipase, high (U/L)	
Missing	NA
Blood urea nitrogen, high (mg/dL)	
Level 1 (>23)	5/65 (7.7)
Level 2 (>27)	1/65 (1.5)
Level 3 (>31)	0/65 (0)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 2 years.
Abbreviations: CPK, creatine phosphokinase; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; NA, not applicable; SC, subcutaneous

There were no clinically significant patterns, trends, or differences from subjects rolled over from Study 2001 (see Section 7.6.1.6) observed in abnormalities in hematology analyte values.

Table 49. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Laboratory Parameter	IV-SC (1705) N=65 n/N_w (%)
Complete Blood Count	
WBC, low (cells/uL)	
Level 1 (<3500)	3/65 (4.6)
Level 2 (<3000)	3/65 (4.6)
Level 3 (<1000)	0/65 (0)
WBC, high (cells/uL)	
Level 1 (>10800)	10/65 (15.4)
Level 2 (>13000)	4/65 (6.2)
Level 3 (>15000)	2/65 (3.1)
Hemoglobin, low (g/dL)	
Level 2 (>1.5 g/dL dec. from baseline)	10/61 (16.4)
Level 3 (>2 g/dL dec. from baseline)	4/61 (6.6)
Hemoglobin, high (g/dL)	
Level 2 (>2 g/dL inc. from baseline)	2/61 (3.3)
Level 3 (>3 g/dL inc. from baseline)	0/61 (0)
Platelets, low (cells/uL)	
Level 1 (<140000)	2/65 (3.1)
Level 2 (<125000)	1/65 (1.5)
Level 3 (<100000)	0/65 (0)
WBC Differential	
Lymphocytes, low (cells/uL)	
Level 1 (<1000)	25/65 (38.5)
Level 2 (<750)	13/65 (20.0)
Level 3 (<500)	6/65 (9.2)
Lymphocytes, high (cells/uL)	
Level 1 (>4000)	2/65 (3.1)
Level 2 (>10000)	0/65 (0)
Level 3 (>20000)	0/65 (0)
Neutrophils, low (cells/uL)	
Level 1 (<2000)	8/65 (12.3)
Level 2 (<1000)	1/65 (1.5)
Level 3 (<500)	0/65 (0)
Eosinophils, high (cells/uL)	
Level 1 (>650)	2/65 (3.1)
Level 2 (>1500)	0/65 (0)
Level 3 (>5000)	0/65 (0)
Coagulation Studies	
PT, high (sec)	
Level 1 (>1.1X ULN)	4/65 (6.2)
Level 2 (>1.3X ULN)	1/65 (1.5)
Level 3 (>1.5X ULN)	0/65 (0)
PTT, high (sec)	
Level 1 (>1X ULN)	16/65 (24.6)
Level 2 (>1.21X ULN)	5/65 (7.7)
Level 3 (>1.41X ULN)	1/65 (1.5)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 2 years.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; SC, subcutaneous; ULN, upper limit of normal; WBC, White blood cells

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of liver laboratory abnormalities for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following tables. There were no clinically significant patterns or trends observed in abnormalities in liver chemistry.

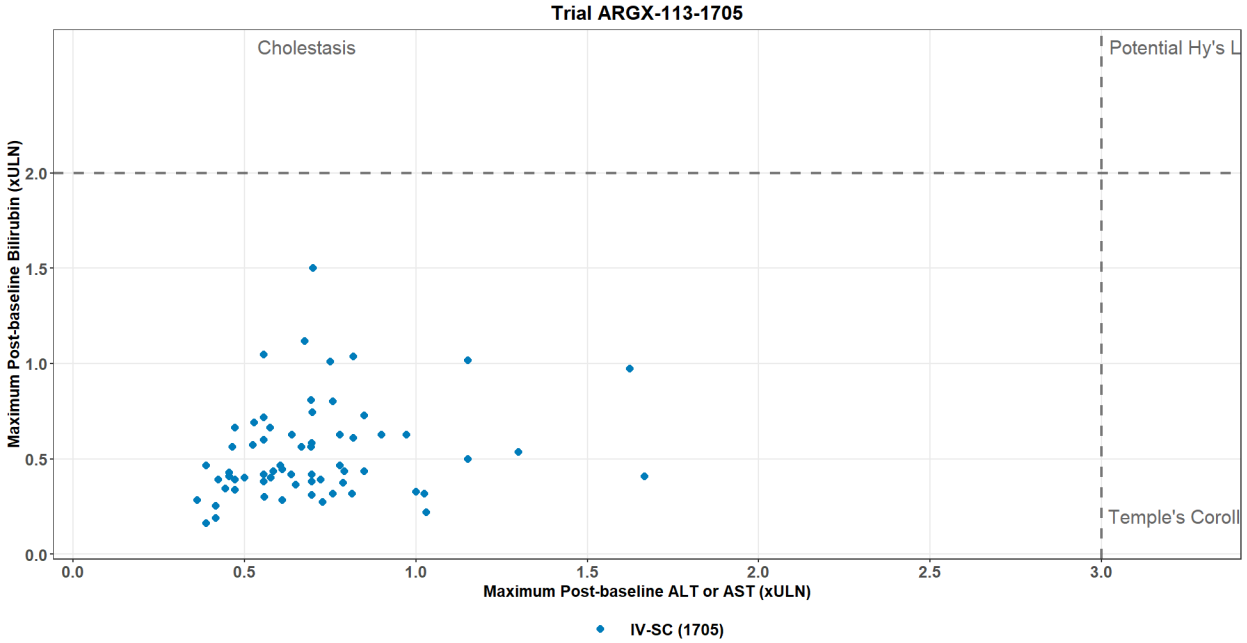
Table 50. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Laboratory Parameter	IV-SC (1705) N=65 n/N_w (%)
Alkaline phosphatase, high (U/L)	
Level 1 (>1.5X ULN)	0/65 (0)
Level 2 (>2X ULN)	0/65 (0)
Level 3 (>3X ULN)	0/65 (0)
Alanine aminotransferase, high (U/L)	
Level 1 (>3X ULN)	0/65 (0)
Level 2 (>5X ULN)	0/65 (0)
Level 3 (>10X ULN)	0/65 (0)
Aspartate aminotransferase, high (U/L)	
Level 1 (>3X ULN)	0/65 (0)
Level 2 (>5X ULN)	0/65 (0)
Level 3 (>10X ULN)	0/65 (0)
Bilirubin, total, high (mg/dL)	
Level 1 (>1.5X ULN)	0/65 (0)
Level 2 (>2X ULN)	0/65 (0)
Level 3 (>3X ULN)	0/65 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 2 years.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot...” and “Cholestatic Drug-Induced Liver Injury Screening Plot...” and the tables “Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot...” and “Subjects in Each Quadrant for Cholestatic DILI Screening Plot…”
Abbreviations: DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous; ULN, upper limit of normal

The following figure and table show a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no Hy’s law cases.

Figure 13. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)



Source: adlb.xpt; Software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal

Table 51. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Quadrant	IV-SC (1705) N=65 n/N_w (%)
Potential Hy's Law (right upper)	0/65 (0)
Cholestasis (left upper)	0/65 (0)
Temple's corollary (right lower)	0/65 (0)
Total	0/65 (0)

Source: adlb.xpt; Software: R
Abbreviations: DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous

7.6.2.8. Vital-Sign Analyses, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

There were no clinically significant patterns or trends observed in abnormalities in vital signs (including diastolic and systolic blood pressure, pulse rate, and temperature) for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod). Respiratory rate data were not included in vital signs datasets.

Table 52. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Systolic Blood Pressure (mm Hg)	IV-SC (1705) N=65 n/N_w (%)
<90	0/62 (0)
≥90	62/62 (100)
≥120	51/62 (82.3)
≥140	15/62 (24.2)
≥160	0/62 (0)
≥180	0/62 (0)

Source: advs.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SC, subcutaneous

Table 53: Percentage of Subjects With Meeting Specific Hypotension Levels Post-Baseline, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Blood Pressure (mm Hg)	IV-SC (1705) N=65 n/N_w (%)
SBP <90	0/62 (0)
DBP <60	4/62 (6.5)

Source: advs.xpt; Software: R
Abbreviations: DBP, diastolic blood pressure; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SBP, systolic blood pressure; SC, subcutaneous

7.6.2.9. Subgroup Analyses, Study 2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Results of the FDA analysis of SAEs and AEs by demographic subgroup for subjects who rolled over to the open-label extension Study 2002 from the supportive open-label extension Study 1705 (from the approved IV form of efgartigimod) are shown in the following tables.

Table 54. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Characteristic	IV-SC (1705) N=65 n/N_s (%)
Sex, n (%)	
Female	2/48 (4.2)
Male	2/17 (11.8)
Age group, years, n (%)	
≥65 years	2/9 (22.2)
18 to 64 years	2/56 (3.6)
Age group ≥75, years, n (%)	
≥75	1/1 (100)
Race, n (%)	
Asian	0/7 (0)
Black or African American	1/2 (50.0)
White	3/56 (5.4)
Ethnicity, n (%)	
Not Hispanic or Latino	4/65 (6.2)

Source: adae.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SC, subcutaneous

Table 55. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study ARGX-113-2002 (Subjects Rolled Over From Study ARGX-113-1705 Only)

Characteristic	IV-SC (1705) N=65 n/N_s (%)
Sex, n (%)	
Female	40/48 (83.3)
Male	9/17 (52.9)
Age group, years, n (%)	
≥65 years	5/9 (55.6)
18 to 64 years	44/56 (78.6)
Age group ≥75, years, n (%)	
≥75	1/1 (100)
Race, n (%)	
Asian	4/7 (57.1)
Black or African American	2/2 (100)
White	43/56 (76.8)
Ethnicity, n (%)	
Not Hispanic or Latino	49/65 (75.4)

Source: adae.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SC, subcutaneous

There were no clinically significant differences in the proportions of subjects with AEs or SAEs as a function of age or sex subgroup. There was also no clinically significant difference in the proportion of subjects with AEs as a function of race or ethnicity, although the small numbers of subjects in these subgroups make the result difficult to interpret.

7.7. Key Safety Review Issues

7.7.1. Infections

Issue

The proposed product consists of two drugs which both carry a risk of infection or spreading of localized infection as described in their respective prescribing information (PI).

Background

Spread of localized infection is listed in the Warnings and Precautions of the Hylenex (hyaluronidase human injection) PI. Infections are also listed in the Warnings and Precautions of the Vyvgart (efgartigimod IV injection) PI.

Assessment

A serious adverse event of cellulitis (right leg) occurred in one (2%) subject in the efgartigimod PH20 SC group in Study 2001. However, causality assessment is confounded by this subject's [redacted](b) (6) prior history of right leg infection (cellulitis), peripheral neuropathy, Type 2 diabetes, right great toe ulcer, lower extremity edema, and concomitant use of immunosuppressant medication (mycophenolate mofetil). There were no events of cellulitis in the efgartigmod IV group or in any subjects in Study 2002.

Adverse events of the infections and infestations system organ class (SOC) occurred in 18% (10 of 55 subjects) of the efgartigimod PH20 SC group versus 20% (11 of 55 subjects) of the efgartigimod 10 mg/kg IV group in Study 2001. The following table shows the individual adverse events by infections and infestations SOC and FDA Medical Query (Broad). There were more subjects with nasopharyngitis (7%) in the efgartigimod PH20 SC group than in the efgartigimod 10 mg/kg IV group (0%).

Table 56: Individual Adverse Events by Infections and Infestations SOC and FDA Medical Query (Broad). Safety Population, Studies ARGX-113-2001 and ARGX-113-2002.

	ARGX-113-2001			ARGX-113-2002		
System Organ Class FMQ (Broad)	EFG SC N=55 n (%)	EFG IV N=55 n (%)	Risk Difference (%) (95% CI)	SC-SC (2001) N=51 n (%)	IV-SC (2001) N=48 n (%)	Total N=99 n (%)
Infections and infestations (SOC)						
Nasopharyngitis	4 (7.3)	0	7.3 (0.4, 14.1) *	8 (15.7)	4 (8.3)	12 (12.1)
Fungal infection	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Opportunistic infection	0	1 (1.8)	-1.8 (-5.3, 1.7)	0	0	0
Viral infection	3 (5.5)	4 (7.3)	-1.8 (-10.9, 7.3)	13 (25.5)	11 (22.9)	24 (24.2)
Bacterial infection	4 (7.3)	6 (10.9)	-3.6 (-14.4, 7.1)	4 (7.8)	3 (6.2)	7 (7.1)
Pneumonia	0	2 (3.6)	-3.6 (-8.6, 1.3)	1 (2.0)	3 (6.2)	4 (4.0)
Renal and urinary disorders (SOC)						
Renal & urinary tract infection	2 (3.6)	3 (5.5)	-1.8 (-9.6, 6.0)	1 (2.0)	1 (2.1)	2 (2.0)

Source:FDA Analysis
Abbreviations: FMQ, FDA Medical Query; IV, intravenous; SC, subcutaneous; SOC, system organ class

Conclusion

There appears to be a similar risk of infections in the efgartigimod PH20 SC and efgartigimod 10 mg/kg IV groups (18% and 20%, respectively). The risk of infections should be included in the Warnings and Precautions section of the efgartigimod PH20 SC prescribing information.

7.7.2. Hypersensitivity

Issue

The proposed product consists of two drugs which both carry a risk of hypersensitivity as described in their respective prescribing information.

Background

Allergic and anaphylactic-like reactions are listed in the Adverse Reactions of the Hylenex (hyaluronidase human injection) prescribing information. Hypersensitivity Reactions (angioedema, dyspnea, and rash) are listed in the Warnings and Precautions of the Vyvgart (efgartigimod IV injection) prescribing information.

Assessment

Adverse events of hypersensitivity (FDA Medical Query (Broad)) occurred in 18% (10 of 55 subjects) of the efgartigimod PH20 SC group versus 4% (2 of 55 subjects) of the efgartigimod 10 mg/kg IV group in Study 2001. The following table compares adverse events related to hypersensitivity in Study 2001 in the efgartigimod PH20 SC and efgartigimod IV groups.

Table 57. Adverse Events Related to Hypersensitivity in Study ARGX-113-2001

Adverse Event	Efgartigimod PH20 SC N=55 N (%)	Efgartigimod IV N=55 N (%)
Hypersensitivity (FDA Medical Query Broad))	10 (18.2)	2 (3.6)
Rash (FMQ)	9 (16.4)	3 (5.5)
Urticaria (FMQ)	2 (3.6)	1 (1.8)
Dyspnea (FMQ Broad)	1 (1.8)	1 (1.8)
Angioedema	0	0
Anaphylaxis	0	0
Edema	0	0

Source: FDA Analysis
Abbreviations: FMQ, FDA medical query; SC, subcutaneous

There was one (2%) SAE of dyspnea in the efgartigimod PH20 SC group (subject # (b) (6)) and one (2%) in the efgartigimod 10 mg/kg IV group (subject # (b) (6)). The former subject (b) (6) had a prior history of asthma and shortness of breath and developed dyspnea in the setting of worsening myasthenia gravis one month after the last efgartigimod SC dose. The latter subject (b) (6) had a history of hypertension, diabetes mellitus, and ankylosing spondylitis and developed chest pain with elevated cardiac enzymes, normal ECG, hypoxemia, and dyspnea one day after the last dose of efgartigimod IV. The chest pain resolved in one day and the dyspnea resolved in 13 days. There is no difference in the rates of dyspnea SAEs between the SC and IV formulations of efgartigimod and the two reported dyspnea SAEs do not have a clear causal association with efgartigimod because of confounding comorbidities in both cases and a delayed onset relative to the last efgartigimod SC dose in the former case.

No anaphylactic reactions or severe or serious cases of hypersensitivity occurred in studies 2001 or 2002.

Conclusion

There are more hypersensitivity-related adverse events in the efgartigimod PH20 SC group than in the efgartigimod IV group in Study 2001. There were no cases of anaphylaxis in either group. Hypersensitivity Reactions (dyspnea, urticaria, and rash) should be listed in the Warnings and Precautions of the efgartigimod PH20 SC prescribing information.

7.7.3. Injection Site Reactions

Issue

There was a higher frequency of injection (local administration) site reactions in subjects who received efgartigimod PH20 SC compared to subjects who received efgartigimod IV in Study 2001.

Background

Local administration reactions FDA medical query (FMQ) occurred in 38% (21 of 55) of subjects who received efgartigimod PH20 SC compared to 6% (3 of 55) of subjects who received efgartigimod IV in Study 2001.

Assessment

The following table shows rates of individual injection site reactions that were observed in Study 2001.

Table 58. Subjects With Injection Site Reaction Adverse Events, Safety Population, Study ARGX-113-2001

Adverse Event	Efgartigimod PH20 SC N=55 N (%)	Efgartigimod IV N=55 N (%)
Injection site rash	8 (14.5)	0
Injection site erythema	7 (12.7)	0
Injection site pruritus	5 (9.1)	0
Injection site bruising	4 (7.3)	0
Injection site pain	3 (5.5)	0
Injection site urticaria	2 (3.6)	0

Source: FDA Analysis
Abbreviations: IV, intravenous; SC, subcutaneous

Conclusion

There are more injection site reactions in the efgartigimod PH20 SC group than in the efgartigimod IV group in Study 2001. Injection site reactions (rash, erythema, pruritus, bruising, pain, and urticaria) should be listed in the efgartigimod PH20 SC prescribing information.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Hepatic Impairment

No dedicated hepatic impairment study was performed. However, efgartigimod is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids, and hepatic impairment is not expected to affect efgartigimod PK. Therefore, the review team agrees with the Applicant's recommendation that no dose adjustment is needed in patients with hepatic impairment.

Although allowed to be enrolled as per the inclusion/exclusion criteria, no subjects with gMG and hepatic impairment have been enrolled in clinical studies with efgartigimod, and no clinical data in subjects with hepatic impairment are available. The impact of hepatic impairment on the PK and PD of efgartigimod has not been studied. Markers of hepatic function were evaluated as potential covariates in the population PK/PD analysis. Albumin, total bilirubin, AST, ALP, and ALT did not influence any of the model parameters in the final population PK/PD model.

Please refer to the clinical pharmacology review of BLA 761195 by Dr. Gopichand Gottipati for additional details.

8.1.2. Renal Impairment

No dedicated pharmacokinetic study has been performed in subjects with renal impairment. No dose adjustment of Vyvgart Hytrulo is needed for patients with mild renal impairment.

With a molecular weight of approximately 54 kDa, efgartigimod is at the boundary of the size of molecules that are renally filtered. Although renal elimination is a minor excretion pathway for efgartigimod (<0.1% dose excreted in urine unchanged), the Applicant's pop-PK analysis suggested that the subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 to <90 mL/min/1.73 m^2) had an approximately 1.22-fold (90%CI: 1.13, 1.30) increase in AUC compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2), which is not clinically significant.

There are insufficient data to evaluate the impact of moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2) and severe renal impairment (eGFR <30 mL/min/1.73 m^2) on the PK and PD of efgartigimod. Therefore, no dose adjustment recommendations can be provided in these subjects.

Please refer to the clinical pharmacology review of BLA 761195 by Dr. Gopichand Gottipati for additional details.

8.1.3. Other Intrinsic Factors

The population PK analyses indicated that age and race did not affect efgartigimod PK, and the effect of sex on efgartigimod PK exposure was minimal and not clinically relevant. Please refer to the clinical pharmacology review of BLA 761195 by Dr. Gopichand Gottipati. The Applicant recommends that dose adjustments are not warranted based on these factors, and the review team agrees with the recommendation.

8.2. Extrinsic Factors

8.2.1. Drug-Drug Interactions

The coadministration of rHuPH20 had limited effect on the PK of efgartigimod (refer to Appendix 14.2.1).

Clinical drug interaction studies have not been performed with efgartigimod. Efgartigimod is not subject to disposition via CYP450 metabolism and traditional drug-transporter-mediated pathways, and therefore drug-interaction liabilities with CYP enzyme or transporter modulators are not expected. In addition, therapeutic antibodies with no increased binding affinity to FcRn are not expected to affect the interaction of efgartigimod with the FcRn receptor.

Concomitant use of efgartigimod PH20 SC with medications that bind to the human neonatal Fc receptor (FcRn) (e.g., immunoglobulin products, monoclonal antibodies, or antibody derivates containing the human Fc domain of the IgG subclass) may lower systemic exposures and reduce

effectiveness of such medications. The review team recommends closely monitoring for reduced effectiveness of medications that bind to the human FcRn. When concomitant long-term use of such medications is essential for patient care, consider discontinuing Vyvgart Hytrulo and using alternative therapies.

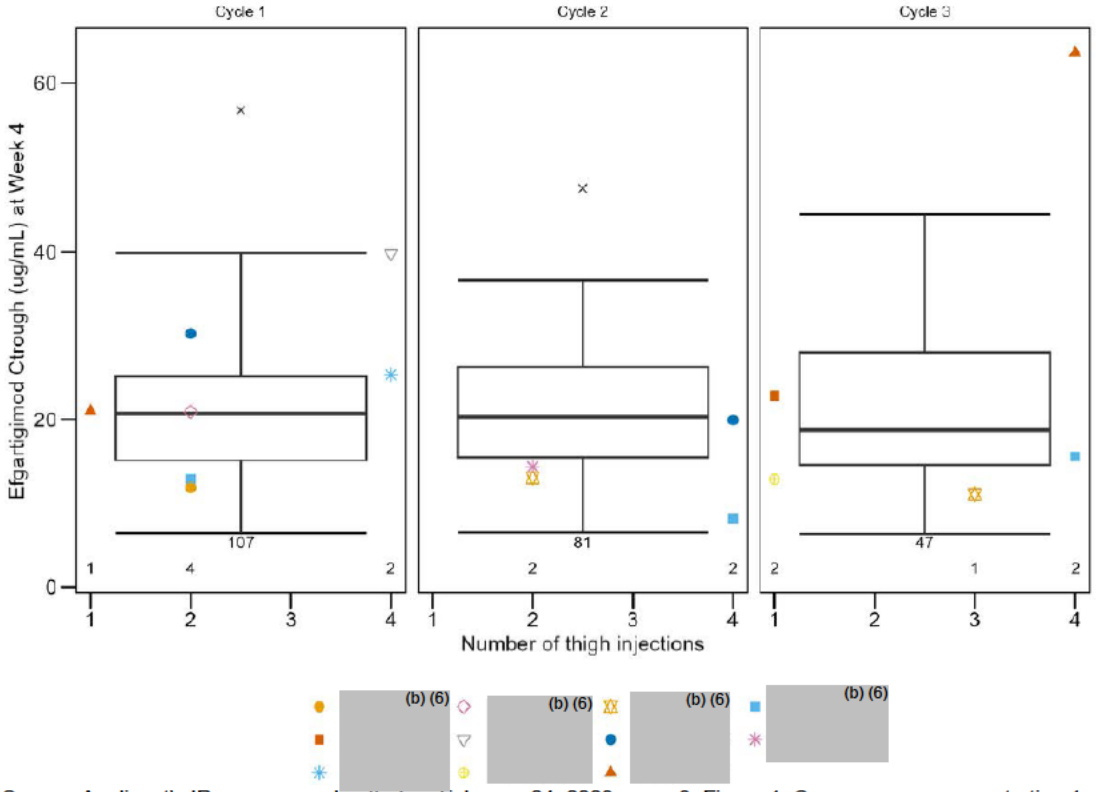
Please refer to the BLA 761195 integrated review Section 8.2 for additional details on the evaluation of drug interactions for efgartigimod.

8.2.2. Injection Site

The impact of efgartigimod PH20 SC injection site (abdomen versus thigh) on PK and PD was evaluated based on data from Study ARGX-113-2002. Up to the bioanalytical data cutoff date of January 12, 2022 (interim analysis 1), 12 (7.65%) subjects had at least one efgartigimod PH20 SC injection into the thigh in the first, second, or third cycle. PK samples were taken at study baseline and one week after the fourth administration (day 29) of each treatment cycle.

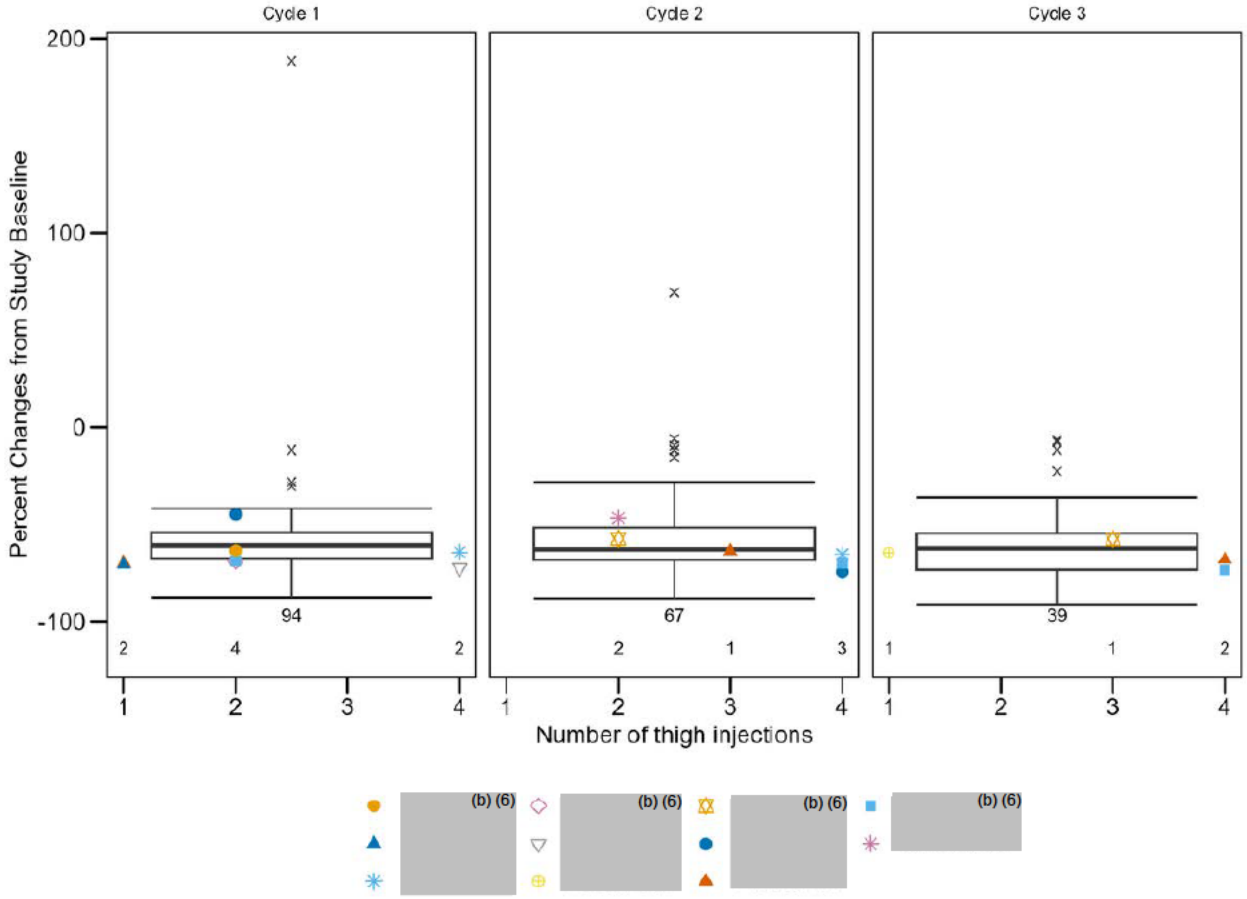
To evaluate the effect of injection site on PK, the available individual efgartigimod C_{trough} at week 4 of subjects (N=11) receiving at least one thigh injection during a cycle were overlaid on a boxplot of efgartigimod C_{trough} at week 4 from subjects with all abdominal injections of efgartigimod PH20 SC (Figure 14). The effect of injection site on AChR-Ab reduction was evaluated using a similar approach (Figure 15). Overall, efgartigimod C_{trough} at week 4 and the percent change from baseline in AChR-Ab at week 4 in subjects with at least one thigh injection during a cycle was comparable with that in subjects after abdominal injections. The review team concluded that the injection site is not expected to significantly affect the PD and efficacy. Thus, the proposed labeling instruction of injection of efgartigimod PH20 SC into the abdomen or thigh (upper leg) is considered acceptable.

Figure 14. Individual Efgartigimod C_{trough} (µg/mL) at Week 4 by Cycle for Subjects With at Least One Thigh Injection in ARGX-113-2002



Source: Applicant's IR response submitted on February 24, 2023, page 3, Figure 1. C_{trough} = serum concentration 1-week after the 4th injection (i.e., week 4); IQR = interquartile range; Note: Individual symbols represent the available observations from subjects who received at least 1 thigh injection. They are vertically grouped by the number of thigh injections received during that cycle. The boxplot summarizes the observations from subjects with only abdominal injections of efgartigimod PH20 SC during that cycle. The solid line is the median, the ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile. The "x" indicates the outliers. The fourth injection of efgartigimod PH20 SC was injected in the thigh across cycles, with the exception of subjects (b) (6) (cycle 3), (b) (6) (cycle 1), and (b) (6) (cycle 2).

Figure 15. Percent Change From Study Baseline in AChR-Ab at Week 4 by Cycle for AChR-Ab Seropositive Subjects With at Least One Thigh Injection in ARGX-113-2002



Source: Applicant's IR response submitted on February 24, 2023, page 5, Figure 3. IQR = interquartile range; Note: Individual symbols represent the available observations from subjects receiving at least 1 thigh injection. They are vertically grouped by the number of thigh injections received during that cycle. The boxplot summarizes the observations from subjects with only abdominal injections of efgartigimod PH20 SC during that cycle. The solid line is the median, the ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile. The "x" indicates the outliers. The fourth injection of efgartigimod PH20 SC was injected in the thigh across cycles, with the exception of subjects (b) (6) (cycle 3), (b) (6) (cycle 1), (b) (6) (cycle 2), and (b) (6) (cycle 1).

8.3. Plans for Pediatric Drug Development

Not applicable. Because efgartigimod was granted orphan drug designation, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

There are no safety data on the use of efgartigimod in pregnant women. No adverse reproductive or developmental effects were observed in a complete battery of reproductive and developmental toxicology studies in Sprague-Dawley rat and New Zealand White rabbit at intravenous doses of 0, 30, and 100 mg/kg QD.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) has assessed BLA 761304 and associated BLA for further manufacturing (BLA 761313) and has determined that the applications meet all applicable standards to support the approval of efgartigimod alfa and hyaluronidase-qvfc. The data and information submitted in the applications were adequate to support the conclusion that the manufacture of efgartigimod alfa and hyaluronidase-qvfc is well-controlled and leads to a product that is pure and potent for the duration of the product shelf-life. OPQ recommends that this product be approved for human use under the conditions specified in the package insert.

9.1. Device or Combination Product Considerations

Not applicable

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Review of the financial disclosures did not raise any concerns about the validity or reliability of the data.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of Study ARGX-113-2001 at Wielospecjalistyczna Poradnia Lekarska, Katowice, Poland. The study appears to have been conducted adequately, and the data generated by the site and submitted by the Applicant appear acceptable in support of the respective indication.

See Section 22 for the clinical inspection report.

11. Advisory Committee Summary

An advisory committee was not held during this marketing application review.

11.1. Summary Review of Studies Submitted With the Investigational New Drug Application

In a WRO dated December 4, 2020 under IND 132953, it was agreed that the nonclinical data package supporting the IV product approval would be sufficient to support the SC submission if comparability were established between the material used in the pivotal nonclinical studies and the to-be-marketed product, a letter of authorization (LOA) were provided to the nonclinical studies of rHuPH20, and plasma efgartigimod exposures in the pivotal nonclinical studies provided adequate safety margins compared to that in humans at the maximum proposed dose in humans. These conditions have been met.

According to the Applicant and as confirmed by the FDA chemist, the material used in toxicology studies, both IV and SC, was comparable to that used in human clinical trials and the to-be marketed product.

A LOA to cross reference BLA 761313 for rHuPH20 and BLA 21859 for Hylenex recombinant (hyaluronidase human injection, approved December 12, 2005) was provided. The highest dose tested (2 mg/kg SC q7d; 220000 U/kg; HED: 0.65 mg/kg or 70968 U/kg) in the chronic 39-week toxicology study of rHuPH20 in cynomolgus monkey (Halozyme Study R09050, BLA 21859), which was an no observed adverse effect level (NOAEL), is 380X the proposed clinical dose of 11200 U of rHuPH20 on a mg/m2 basis. Based on the expected minimal systemic exposure documented in humans, no carcinogenicity studies of rHuPH20 were conducted.

Based on the plasma efgartigimod levels measured at the HD of 100 mg/kg/week in the 26-week IV toxicity study in cynomolgus monkey submitted to BLA 761195 ([maximum concentration] C_{max} and AUC_{tau} of 2653/2563 µg/mL and 30481/32130 µg.h/mL in male/female) and human data from clinical study ARGX-113-1907 in which 4-weekly doses of 1008 mg were administered SC (C_{max} and AUC_{tau} of 50 µg/mL and 5841 µg.h/mL), exposure multiples for efgartigimod were approximately 52- and 5-fold for C_{max} and AUC, respectively.

The only new safety studies for this submission were a 12-week bridging study in cynomolgus monkeys with weekly SC administration of efgartigimod with and without 2000 U/mL rHuPH20 ((b) (4) Study No. 36930), an 11-week monkey study in which the T-cell dependent antibody response (TDAR) response to IV efgartigimod administration was evaluated (b) (4) # 8459761), and a single IM and SC dose local tolerance study of efgartigimod with rHuPH20 in rabbits ((b) (4) # 37107). Updated PK/PD data, including a single IV or SC dose study in cynomolgus monkeys ((b) (4) Study No. 34856) that is relevant to this application, and an interaction study of efgartigimod when combined with IVIg in Tg32 mice (121510_IVFC) were also submitted.

In the single-dose PK/PD study in monkeys reanalyzed for this submission (in which the impact of the reanalysis was minimal), IV administration of efgartigimod (20 mg/kg) drug substance from two difference batches (454915, originating from clone (b) (4) and used in the chronic IV monkey toxicity study, and 590157, originating from clone (b) (4) used in the nonclinical and clinical studies for the SC submission) produced comparable decreases in IgG levels. SC administration of the same dose of efgartigimod (batch 590156, also derived from clone (b) (4)) resulted in a slightly higher C_{min} value compared to IV administration, but levels were more variable in the SC group. The time to reach a maximum PD effect was 5 to 7 days and was comparable among the 3 groups. Similar PK profiles were also observed following single IV administration of the different batches. SC administration resulted in a bioavailability of around 50% compared to IV administration; the C_{max} was approximately one-tenth lower with SC administration and was reached 24 to 48 hours after dosing.

Because intravenous immunoglobulin (IVIg) is used to treat autoimmune conditions like myasthenia gravis, the potential for interaction between therapeutic IVIg and efgartigimod was examined in human neonatal Fc receptor (FcRn) transgenic mice (Tg32 mice) which express human FcRn and lack the expression of endogenous mouse FcRn. Administration of efgartigimod (20 mg/kg IV) to Tg32 mice 3 days after a therapeutic 2 g/kg (IP) dose of IVIg resulted in a rapid PD effect on reconstituted circulating human IgG (hIgG) and human IgG1 (Hulys11) tracer levels, consistent with the intended MOA. Treatment with IVIg did not appear

to affect the PK profile of efgartigimod based on comparison with previous data in Tg32 mice described in the IV submission.

In the 12-week bridging study in cynomolgus monkeys, SC administration of efgartigimod (0 (formulation buffer), 30, or 100 mg/kg q7d) with 2000 U/mL rHuPH20 or efgartigimod (100 mg/kg q7d) alone produced no mortality, clinical signs, or BW effects. Enlarged lymph nodes associated with increased severity of lymphoid hyperplasia was seen in efgartigimod-treated animals (both with and without rHuPH20) at the end of the dosing and recovery periods. This was attributed to an immune response to the foreign protein not expected to be predictive for humans. Injection site histopathological changes were also seen in animals treated with efgartigimod, with or without rHuPH20. None of these effects were considered adverse. Anti-efgartigimod antibodies were detected by Day 15 or 29, but there was no dose-response, and efgartigimod exposures did not appear to be significantly affected. The NOAEL for systemic effects was 100 mg/kg efgartigimod with or without 2000 U/mL rHuPH20.

rHuPH20 appeared to have the intended effect of increasing efgartigimod exposures, although the differences were not large. After the last SC dose of 100 mg/kg with 2000 U/mL rHuPH20, C_{max} and $AUC_{0\text{-}144h}$ were 585/402 µg/mL and 34030/22182 µg.h/mL in males/females, respectively. After the last SC dose of 100 mg/kg without rHuPH20, C_{max} and $AUC_{0\text{-}144h}$ were 377/378 µg/mL and 25143/19973 µg.h/mL in males/females, respectively. Exposures in this study were similar to those measured in the chronic IV toxicity study in monkeys at the same weekly 100 mg/kg dose ($AUC_{0\text{-}168h}$ of 30481/32130 µg.h/mL in male/female), which was the highest dose tested and the NOAEL in that study. The results of this study do not indicate any unique effects of the new formulation, combination, or route and did not change the conclusions from the IV submission.

An 11-week study of the TDAR response to IV efgartigimod administration in monkeys had been submitted with the IV application in the EU but not previously submitted to the FDA. Once weekly IV (bolus) administration of a dose of 100 mg/kg to cynomolgus monkeys for 11 weeks was well tolerated and resulted in transient reductions in the anti-KLH IgG antibody response and total IgG antibody titers that showed reversal during the recovery period. The antigen specific T-cell response as measured in an IFN-γ ELISPOT assay appeared to be unaffected by efgartigimod. The dose of 100 mg/kg q7d was associated with C_{max} values of 3260 and 3330 µg/mL and $AUC_{0\text{-}168h}$ values of 32400 and 30900 h*µg/mL in males and females, respectively. The results of this study are consistent with those described in the IV submission.

In the single-dose local tolerance study in rabbits, administration of efgartigimod (180 mg/mL) with rHuPH20 (2039 U/mL) by the IM (0.25 mL) and SC (1 mL) routes resulted in no drug-related macroscopic or microscopic changes at the injection sites.

III. Additional Analyses and Information

12. Summary of Regulatory History

Vyvgart (efgartigimod alfa-fcab) (also called ARGX-113) injection for intravenous (IV) use was developed by argenx under investigational new drug (IND) 132953 and approved under BLA 761195 on December 17, 2021. Vyvgart is a neonatal Fc receptor blocker indicated for the

treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Argenx developed a subcutaneous (SC) formulation of efgartigimod which contains recombinant human hyaluronidase (rHuPH20). The SC formulation was developed as a ready-to-use solution for injection in a single dose vial to be administered once weekly for 4 weeks. Efgartigimod with rHuPH20 is a fixed-combination product per 21 CFR 300.50 because both efgartigimod and hyaluronidase are considered active ingredients. The contribution of hyaluronidase is to serve as a permeation enhancer and facilitate absorption of efgartigimod.

Efgartigimod rHuPH20 for SC administration was first discussed in a Type C Written Response Only dated December 4, 2020, under IND 132953. The Applicant was informed that rHuPH20 is an active ingredient and would require its own BLA for further manufacturing (BLA FFM) (b) (4)

IND 152843 was submitted on December 23, 2020, for the use of efgartigimod rHuPH20 for the treatment of myasthenia gravis. The initial IND included protocol ARGX-113-2001, entitled, "A Phase 3, Randomized, Open-Label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC with Multiple Intravenous Infusions of Efgartigimod in Patients with Generalized Myasthenia Gravis (ADAPTSC)." A may proceed letter was sent on January 22, 2021, reiterating the Divisions recommendations from the December 4, 2020, written responses under IND 132953. The may proceed letter documented the Division's concerns that there was not enough information to set a non-inferiority margin (b) (4)

The Applicant submitted a request for human factors (HF) validation protocol review on July 8, 2021. The request was withdrawn on August 4, 2021, because the Applicant conducted a formative HF study first to inform the design of the HF validation study. The revised HF validation protocol was submitted on October 14, 2021, and advice on the HF validation protocol was provided by the Division of Medication Error Prevention and Analysis (DMEPA) on March 22, 2022.

Although an initial pediatric study plan (iPSP) was submitted on October 29, 2021, the iPSP was administratively closed on August 3, 2022, after the Applicant obtained orphan drug designation on July 27, 2022, for the treatment of gMG.

In an email dated October 15, 2021, the Agency agreed that standard carcinogenicity studies would not be feasible. A carcinogenicity waiver assessment was included in the BLA.

The Applicant submitted a request for proprietary name review for "Vyvgart (b) (4)" to the IND on March 29, 2022, and again to BLA 761304 on October 14, 2022. DMEPA determined the name request was unacceptable. Argenx submitted another request for proprietary name review to BLA (b) (4) for "Vyvgart Hytrulo" on February 9, 2023, which was determined to be conditionally acceptable on March 16, 2023.

No formal pre-BLA meeting was held under IND 152843. Instead, a Type C teleconference was held on July 12, 2022, to discuss the nonclinical, clinical, and regulatory content of the proposed

BLA. (b) (4)

A Type C CMC-only meeting was held on June 8, 2022, under IND 152843, to discuss the quality sections of the BLA. FDA agreed that additional stability data could be provided to the BLA no later than 30 days after the original BLA submission. That additional stability data was submitted to BLA 761304 on October 19, 2022.

The original BLA 761304 was submitted on September 20, 2022, with the proposed indication for the treatment of generalized myasthenia gravis (gMG). Unlike Vyvgart (BLA 761195), BLA 761304 does not specify for patients AChR antibody positive. Argenx submitted a tropical disease priority review voucher (PRV) acquired from Bayer for this BLA. On the same day, the cross-referenced BLA for further manufacturing (FFM) from Halozyme was submitted to BLA 761313.

13. Pharmacology Toxicology

13.1. Individual Reviews of Studies Submitted With the New Drug Application

See Section 13.1.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

14.2.1. Pharmacokinetics

Key PK parameters of efgartigimod after single and multiple administrations of efgartigimod PH20 SC are summarized in Table 59. The mean C_{max} and $AUC_{0\text{-}168h}$, after the fourth efgartigimod administration, were approximately 78% and 16% lower after efgartigimod PH20 SC 1008 mg administration compared to after administration of efgartigimod IV 10 mg/kg, respectively. C_{trough} was up to 43% higher. The AUC was not demonstrated to be bioequivalent between IV and SC formulations across different body weights (refer to Section 6.1.2).

In line with the observed C_{trough}, the accumulation of efgartigimod PH20 SC over time was minimal.

Table 59. Pharmacokinetics of Efgartigimod Following Subcutaneous Administration With rHuPH20 as Compared to Intravenous Administration

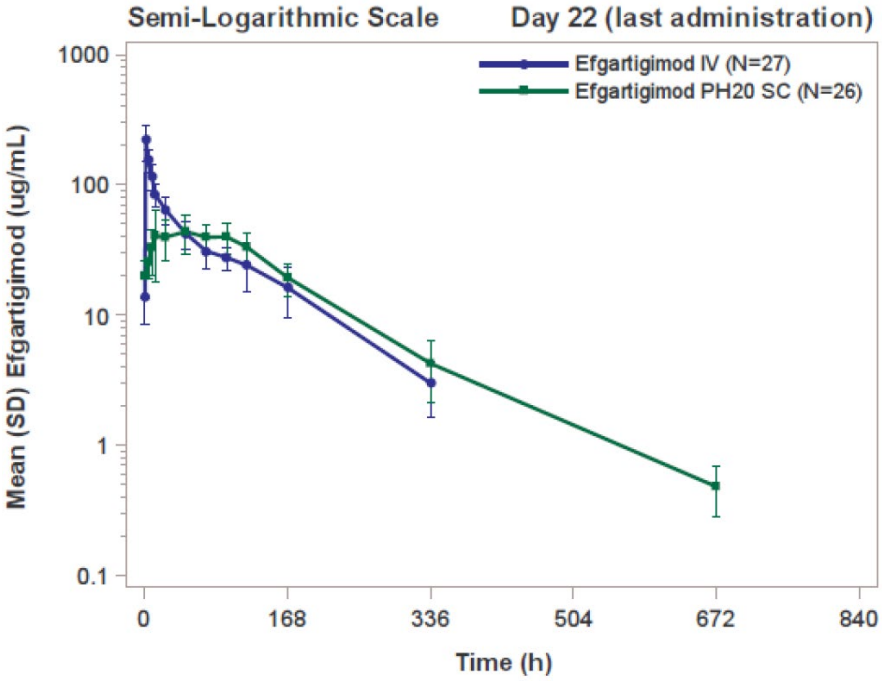
Study	Population	Treatment	n	Single dose PK parameters of efgartigimod						
				C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg.h/mL)	AUC_{0-inf} (µg.h/mL)	$t_{1/2}$ (h)	CL(/F) (L/h)	V_z(/F) (L)
ARGX-113-1901	Healthy participants	A single dose of efgartigimod SC comixed with 2 000 U/mL rHuPH20								
		750 mg	8	31.1 (10.7)	35.99 (11.99-95.99)	3859 (1085)	3947 (1071)	74.9 (10.6)	0.204 (0.0576)	21.9 (6.58)
		1250 mg	8	51.4 (10.7)	36.01 (23.99-71.99)	7330 (1676)	7420 (1686)	73.0 (10.3)	0.177 (0.0399)	18.5 (4.21)
		1750 mg	8	78.4 (10.2)	84.00 (36.00-143.99)	11 124 (1326)	11 195 (1335)	63.8 (2.77)	0.158 (0.0189)	14.6 (1.97)
		10 mg/kg	8	25.6 (12.9)	59.99 (35.99-95.99)	3575 (1199)	3632 (1185)	77.6 (6.83)	0.242 (0.0951)	27.3 (11.4)

Study	Population	Treatment	Study day	Multiple dose PK parameters of efgartigimod							
				C_{trough} (µg/mL)		C_{max} (µg/mL)		t_{max} (h)		AUC_{0-168h} (µg.h/mL)	
				n	Mean (SD)	n	Mean (SD)	n	Median (min-max)	n	Mean (SD)
ARGX-113-1907	Healthy participants	A cycle of 4 weekly administrations of efgartigimod IV									
		10 mg/kg q7d	1	-	*NA*	27	229 (48.1)	27	1.02 (1.00-1.20)	-	*NA*
			8	27	9.41 (3.33)	27	222 (44.9)	27	1.02 (1.00-1.07)	-	*NA*
			15	27	12.7 (4.64)	27	229 (64.1)	27	1.00 (1.00-1.02)	-	*NA*
			22	27	13.8 (5.43)	26	226 (66.1)	26	1.01 (1.00-4.00)	26	6918 (1388)
		A cycle of 4 weekly administrations of efgartigimod PH20 SC									
		1000 mg q7d	1	-	*NA*	-	*NA*	-	*NA*	-	*NA*
			8	26	15.5 (4.33)	-	*NA*	-	*NA*	-	*NA*
			15	23	19.1 (5.25)	-	*NA*	-	*NA*	-	*NA*
			22	26	19.8 (6.09)	25	50.1 (21.2)	25	48.00 (8.00-96.02)	25	5841 (1506)
ARGX-113-2001	Participants with gMG	A cycle of 4 weekly administrations of efgartigimod IV									
		10 mg/kg q7d	1	-	*NA*	54	199 (62.8)	-	*NA*	-	*NA*
			8	48	16.4 (33.0)	52	215 (63.0)	-	*NA*	-	*NA*
			15	49	14.0 (6.92)	53	211 (75.0)	-	*NA*	-	*NA*
			22	49	15.2 (8.05)	52	206 (59.5)	-	*NA*	-	*NA*
			29	51	14.9 (6.43)	-	*NA*	-	*NA*		*NA*
		A cycle of 4 weekly administrations of efgartigimod PH20 SC									
		1000 mg q7d	8	43	18.3 (8.05)	-	*NA*	-	*NA*	-	*NA*
			15	43	21.4 (8.36)	-	*NA*	-	*NA*	-	*NA*
			22	41	22.5 (9.61)	-	*NA*	-	*NA*	-	*NA*
			29	49	22.0 (8.12)	-	*NA*	-	*NA*	-	*NA*
ARGX-113-2002	Participants with gMG[a]	A cycle of 4 weekly administrations of efgartigimod PH20 SC									
		1000 mg q7d (Cycle 1)	29	116	21.5 (8.17)	-	*NA*	-	*NA*	-	*NA*
		1000 mg q7d (Cycle 2)	29	86	20.3 (7.57)	-	*NA*	-	*NA*	-	*NA*
		1000 mg q7d (Cycle 3)	29	52	21.9 (10.7)	-	*NA*	-	*NA*	-	*NA*

Source: Applicant's summary of clinical pharmacology, pages 64-66
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

A representative PK profile following efgartigimod PH20 SC 1008 mg and efgartigimod IV 10 mg/kg administration is presented in Figure 16. The PK profile was obtained after the fourth weekly administration (study day 22) in Study ARGX-113-1907.

Figure 16. Mean Efgartigimod Serum Concentration-Time Profiles After the Fourth Weekly Administration of Efgartigimod PH20 SC 1008 mg or Efgartigimod IV 10 mg/kg in Healthy Subjects



Source: Applicant's summary of clinical pharmacology studies, page 14, Figure 2. Note: PK profile shown after the fourth administration on day 22 of efgartigimod PH20 SC 1008 mg or efgartigimod IV 10 mg/kg.

Dose proportionality of serum efgartigimod concentrations following single SC administrations was evaluated in Study ARGX-113-1901 at the fixed dose range of 750 to 1750 mg (comixed with rHuPH20) by statistical analysis using a power model (Table 60). After a single dose, no evidence of deviation from dose proportionality was observed for C_{max} and $AUC_{0\text{-}inf}$. Overall, the exposures of efgartigimod were approximately dose proportional following a single dose of 750 to 1750 mg efgartigimod rHuPH20 SC.

Table 60. Dose Proportionality in PK of Efgartigimod SC Comixed With rHuPH20 as Assessed by a Power Model

Actual dose range (mg)	Parameter	Slope estimate	95% CI	p-value
735-1763	C_{max}	1.1364	0.828-1.445	0.369
	$AUC_{0\text{-}t}$	1.2793	1.011-1.548	0.042
	$AUC_{0\text{-}inf}$	1.2570	0.994-1.520	0.055

Source: Applicant's summary of clinical pharmacology studies, page 52, Table 14. Note: Dose proportionality was explored using the power model on log-transformed PK parameters. A point estimate and 95% CI were produced for the slope. A slope of 1 (i.e., a 95% CI containing 1) means that no evidence of deviation from dose proportionality was found. The p-value is also presented for the test of the hypothesis H0: slope =1.
Abbreviations: CI, confidence interval; PK, pharmacokinetics; SC, subcutaneous

The effect of rHuPH20 on the PK of efgartigimod was evaluated by comparison of PK parameters after a single dose of efgartigimod SC 10 mg/kg without (Study ARGX-113-1702) or comixed with 2000 U/mL rHuPH20 (Study ARGX-113-1901) in healthy subjects (Table 61). Efgartigimod C_{max} and $AUC_{0\text{-}inf}$ were slightly higher when efgartigimod SC 10 mg/kg was administered with 2000 U/mL rHuPH20 compared with efgartigimod SC without rHuPH20.

Comixed with rHuPH20, mean (SD) C_{max} and $AUC_{0\text{-}inf}$ were 25.6 (12.9) µg/mL and 3632 (1185) µg.h/mL, respectively; whereas, without rHuPH20, C_{max} and $AUC_{0\text{-}inf}$ were 19.4 (9.99) µg/mL and 3260 (1470) µg.h/mL, respectively. The elimination half-life was comparable after SC administration without and comixed with rHuPH20. rHuPH20 is not measurable in the systemic circulation at clinically relevant doses.

Table 61. Comparison of Efgartigimod PK After Single-Dose Administration of 10 mg/kg Efgartigimod SC Without or Comixed With 2000 U/mL rHuPH20 in Healthy Subjects

	10 mg/kg Efgartigimod SC (ARGX-113-1702)	10 mg/kg Efgartigimod + 2000 U/mL rHuPH20 SC (ARGX-113-1901)
n	8	8
C_{max} (µg/mL)	19.4 (9.99)	25.6 (12.9)
t_{max} (h)	107.60 (71.07-120.18)	59.99 (35.99-95.99)
$AUC_{0\text{-}inf}$ (µg.h/mL)	3260 (1470)	3632 (1185)
$t_{½}$ (h)	76.3 (14.2)	77.6 (6.83)

Source: Applicant's summary of biopharmaceutic studies, page 19, Table 3. Note: Values reported are mean (SD), except for t_{max} where median (min-max) is presented.
Abbreviations: C_{max}, maximum plasma concentration; PK, pharmacokinetics; SC, subcutaneous; T_{max}, time to maximum concentration

14.3. Bioanalytical Method Validation and Performance

14.3.1. Bioanalytical Method Validation for Efgartigimod Serum Concentration

A sandwich immunoassay on the Gyrolab Bioaffy system was validated at (b) (4) and used for the determination of efgartigimod in serum samples from ARGX-113-2001 and ARGX-113-2002. Briefly, efgartigimod is captured by biotinylated (b) (4) His and AlexaFluor-647-labeled (b) (4) His is being used for the detection of efgartigimod. Detailed information for the Gyrolab method validation and the in-study method assay performance parameters are provided in Table 62 and Table 63, respectively. The reviewer agrees that the bioanalytical method validation and performance in the pivotal Study 2001 is adequate for quantification of serum efgartigimod concentrations.

In earlier studies 1901 and 1907, the assay used for the determination of efgartigimod in serum samples was a quantitative enzyme-linked immunosorbent assay (ELISA) method validated at (b) (4) (Validation reports: CP185065 and CP190517). In this ELISA method, efgartigimod binds to the capture tool (b) (4), which is a chimeric molecule consisting of an efgartigimod-specific binding variable domain of a llama heavy chain-only antibody clone (b) (4) combined with a mouse crystallized Fc fragment. Efgartigimod was detected using a goat F(ab')2 anti-human Fc antibody labeled with horseradish peroxidase (HRP). The ELISA method was validated in compliance with the standards in the FDA

Bioanalytical Method Validation guidance. The Gyrolab method was cross validated with the ELISA method (ARGX-PTBA-0447).

Table 62. Summary Method Validation for Determination of Efgartigimod in Serum in Study 2001 With Gyrolab Method

Validation Parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Standard calibrators from LLOQ to ULOQ.	8 calibrators, 200 to 5000 ng/mL
	Inter assay accuracy (%bias) from LLOQ to ULOQ	−0.9% to 1.3% (Data presented is from all validation runs)
	Cumulative precision (%CV) from LLOQ to ULOQ	2.1% to 4.7% (Data presented is from all validation runs)
Performance of QCs during accuracy and precision runs	Intra run accuracy (%bias) in 5 QCs	LLOQ (200 ng/mL): −6.5% to 11.5% LQC (500 ng/mL): −27.0% to 10.0% MQC (1400 ng/mL): −19.3% to 3.6% HQC (3750 ng/mL): −21.1% to 7.2% ULOQ (5000 ng/mL): −27.6% to 7.2%
	Inter batch precision %CV	LLOQ (200 ng/mL): ≤7.9% LQC (500 ng/mL): ≤11.8% MQC (1400 ng/mL): ≤9.3% HQC (3750 ng/mL): ≤11.0% ULOQ (5000 ng/mL): ≤14.7%
	Total error (%TE) - Inter batch	LLOQ (200 ng/mL): ≤11.9% LQC (500 ng/mL): ≤12.2% MQC (1400 ng/mL): ≤10.7% HQC (3750 ng/mL): ≤15.5% ULOQ (5000 ng/mL): ≤21.1%
Selectivity, matrix effect, hemolysis effect, lipemic effet, and carry-over	Not significant	
Dilution linearity and hook effect	Dilution linearity was tested with 7 dilution factors up to 1/2000. Bias observed at a dilution of 1/2000 was −0.5% to 2.0% No hook effect was observed.	
Bench-top/process stability	24 hours at room temperature	
Freeze-thaw stability	−75°C ±10°C for 6 freeze-thaw cycles	
Long-term stability	732 days at -20°C and -80ºC	

Source: Applicant's summary of biopharmaceutic studies, page 25, Table 6

Table 63. Summary Method Performance for Determination of Efgartigimod in Serum in Study 2001 With Gyrolab Method

Assay passing rate	49 of the 57 analytical runs passed (84% passing rate)
Standard curve performance	Inter assay bias range: −1.1% to 1.8% Inter assay precision: ≤5.4% CV
QC performance	Inter assay bias range: 2.9% to 4.5% Inter assay precision: ≤8.6% CV
Method reproducibility	Incurred sample re-analysis was performed in 10.0% of study samples, and 87.4% of the samples met the prespecified criteria.

Qualification runs	New standard working stock CRG210650 was successfully bridged. New labeled biotin-(b) (4)His CRG220056 and AlexaFluor-647 (b) (4)His CRG220057 were successfully bridged against the old labeled CRG200338 and CRG200339, respectively
Study sample analysis/stability*	Efgartigimod is stable in human serum for up to 732 days at -20°C and -80°C, which covers the maximum storage duration of the samples in ARGX-113-2001 (238 days).

Source: Applicant's summary of biopharmaceutic studies, page 25, Table 6. *: Long-term stability data were from the Information Request response submitted on March 27, 2023.

14.3.2. Bioanalysis of AChR-Ab in Human Serum

The Applicant used a commercialized kit to quantify the anti-acetylcholine receptor antibody (AChR-Ab) in human serum with a radioimmunoassay (RIA) method. AChR from human muscle is used as antigen. The receptors are labeled with ^{125}I-α-bungarotoxin. AChR-Ab present in human serum attach to the labeled receptors. The resulting immune complexes are precipitated with anti-human IgG. The amount of radioactivity of the sediment is directly proportional to the concentration of AChR-Ab in the sample. The method was validated at (b) (4) and used in study sample analysis for studies ARGX-113-2001. The review team thoroughly reviewed all the relevant information on bioanalysis of AChR-Ab, including the bioanalytical validation report, sample analysis report, and multiple information request responses submitted on January 17, February 17, March 3, March 27, and April 19 in 2023. Overall, the method validation and performance demonstrate that the method is specific, accurate and precise in determining the AChR-Ab concentration in plasma. With the supplemental process and long-term storage stability data using incurred samples, the method was considered adequate to support the sample analysis in Study ARGX-113-2001. Summary of the method validation is presented in Table 64.

Table 64. Bioanalytical Validation for Determination of AChR-Ab in Human Serum by RIA

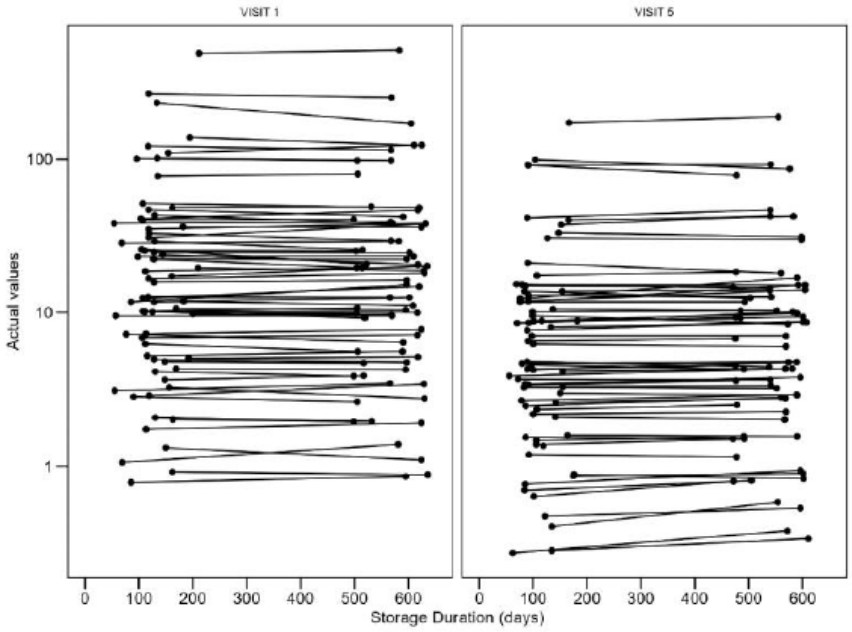
<table>
<tr><td>Method validation report number</td><td>CP155456</td></tr>
<tr><td>Calibration range</td><td>0.200 to 1.50 nmol/L</td></tr>
<tr><td>Calibration standards</td><td>0.100, 0.200, 0.350, 0.500, 0.733, 0.967, 1.20, 1.50, 3.00 and 8.00 nmol/L</td></tr>
<tr><td>Anchoring points</td><td>0.100, 3.00 and 8.00 nmol/L</td></tr>
<tr><td>QC concentrations</td><td>0.265 (QC LLOQ), 0.445 (QC Low), 0.615 (QC Mid), 1.17 (QC High) and 1.49 (QC ULOQ) nmol/L</td></tr>
<tr><td>Lower limit of quantitation (LLOQ)</td><td>0.265 nmol/L</td></tr>
<tr><td>Higher limit of quantitation (ULOQ)</td><td>1.49 nmol/L</td></tr>
<tr><td>QCs accuracy and precision runs</td><td>
<table>
<tr><td rowspan="2">Assay</td><td colspan="2">Imprecision (%CV)</td><td colspan="2">Inaccuracy (%RE)</td></tr>
<tr><td>LLOQ and ULOQ</td><td>Other levels</td><td>LLOQ and ULOQ</td><td>Other levels</td></tr>
<tr><td>Intra-run</td><td><5%</td><td><4%</td><td>Within ±7%</td><td>Within ±8%</td></tr>
<tr><td>Inter-run</td><td><5%</td><td><6%</td><td>Within ±4%</td><td>Within ±3%</td></tr>
</table>
</td></tr>
<tr><td>Interference & specificity</td><td>No drug interference up to 1000 µg/mL efgartigimod</td></tr>
<tr><td>Hemolysis effect*</td><td>No interference from hemolysis</td></tr>
</table>

Lipemic effect *	No clinical samples reported being lipemic
Dilution linearity*	Dilution factor 1/1200
Bench-top/process stability*	15.5 hours at room temperature
Freeze-Thaw stability*	5 freeze/thaw cycles at -75°C
Long-term storage stability*	-75°C for up to 514 days evaluated with incurred sample stability

Source: Applicant's bioanalytical report CP155456. *: Refer to the Information Request responses submitted by Applicant on January 17, February 17, March 3, March 27, and April 19 in 2023.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; RIA, radioimmunoassay

Of note, the long-term storage stability was evaluated using incurred sample stability of 136 clinical study samples from Study ARGX-113-2001 (68 samples predose [baseline, day 1] and 68 samples postdose [visit 5, day 29]). The Applicant repeated the bioanalysis for AChR-Ab using the samples that were previously analyzed with the same assay and compared the concentrations of same clinical samples from the re-analysis to the initial concentrations. Since the initial analysis, the samples had been stored at -75°C ±10°C for 369 to 514 days at the time of re-analysis, which exceeded the initial maximum storage duration of 212 days from sample collection to sample analysis. Figure 17 shows that no obvious change was observed with the AChR-Ab concentrations after extended storage of samples. 96.32% (131 of 136) samples were within ±30.00% difference from the mean of the initial and repeat determinations. These data support the serum sample storage duration for AChR-Ab in Study ARGX-113-2001, in the context of using AChR-Ab as the PD biomarker for bridging between IV and SC formulations.

Figure 17. AChR-Ab Concentrations (nmol/L) at the Initial and Repeat Analysis of the Long-term Stability Assessment



Source: Applicant's IR response submitted on March 27, 2023, page 3, Figure 1. Note: AChR-Ab concentration values (nmol/L) are shown on the y-axis. The left and right graphs show the samples collected from visit 1 (baseline) and visit 5 (day 29), respectively. Solid lines connect the concentration measured at the initial analysis to the concentration measured at re-analysis for each sample.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

14.4.1. ADA and Neutralizing Abs (Nab) Against Efgartigimod

A higher incidence of ADA against efgartigimod was observed in subjects who received efgartigimod PH20 SC compared to efgartigimod IV. In Study 2001, following up to 10 weeks of treatment, the incidence of ADA against efgartigimod was 35% (19 of 55) in the efgartigimod PH20 SC arm. The IV arm had an ADA incidence of 20% (11 of 55), which is consistent with the reported incidence (20%, 17 of 83) from Study 1704 following 26 weeks of efgartigimod IV treatment.

According to Applicant's analysis, in up to 10 weeks of efgartigimod PH20 SC treatment in Study 2001, there was no clear evidence of an impact of ADA against efgartigimod on PK or PD (percent reduction of total IgG) of efgartigimod following SC administration (Figure 18 and Figure 19). In addition, in the efgartigimod PH20 SC arm, similar percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders were observed among subjects who were negative for ADA against efgartigimod (23 of 30, 76.7%) compared with subjects with treatment-induced (13 of 18, 72.2%) or treatment-boosted (1 of 1, 100%) ADA against efgartigimod.

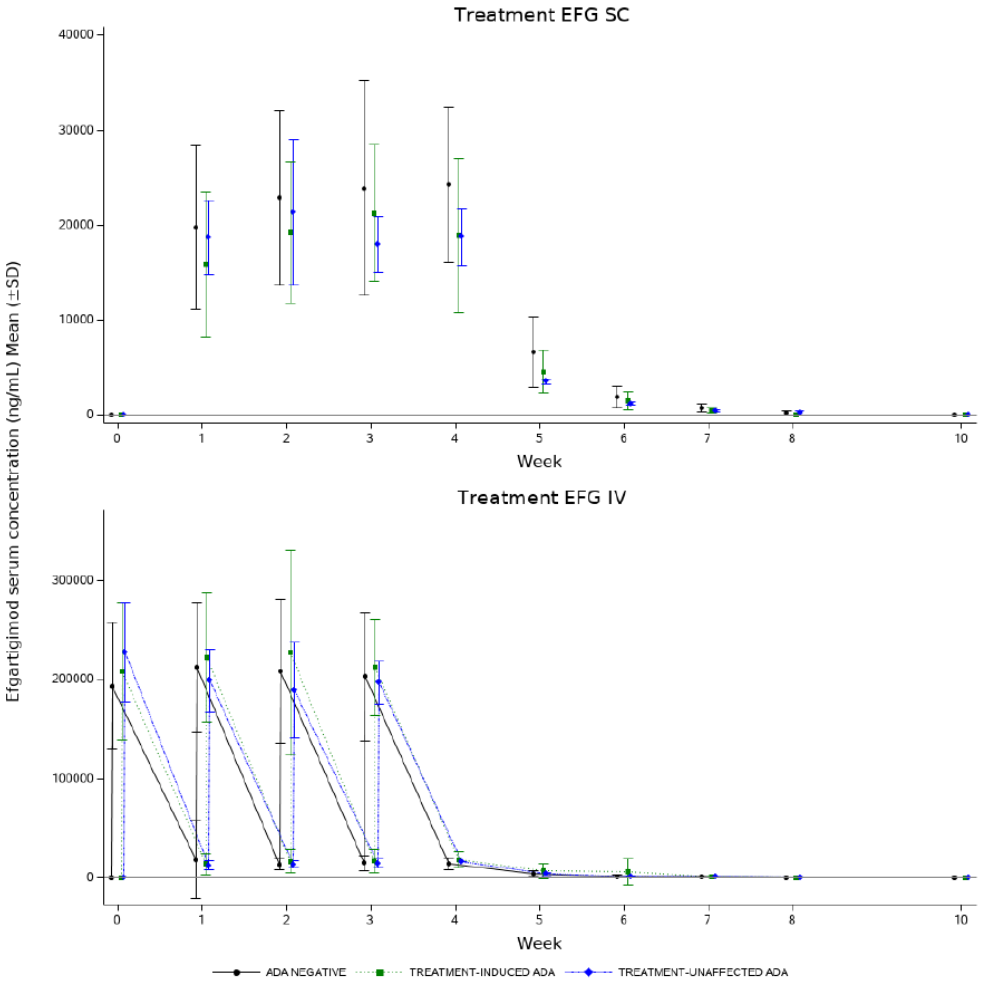
The review team agrees that overall, there was no observed apparent impact of ADA against efgartigimod on PK, PD, or efficacy of efgartigimod PH20 SC. However, given the low number of subjects who tested positive for ADA, the available data are too limited to make definitive conclusions regarding immunogenicity and the effect on pharmacokinetics, safety, or efficacy of efgartigimod PH20 SC.

The Applicant's reported incidence of NAb against efgartigimod was 4% (2 of 55) in both efgartigimod PH20 SC and IV arms. However, the OBP review team noted insufficient sensitivity with NAb assay against efgartigimod. The data interpretability for the incidence of NAb against efgartigimod and its impact is limited by both assay method and number of subjects tested positive for NAb. Please refer to OBP review by Dr. Frederick Mills for additional details.

14.4.2. ADA and NAb Against rHuPH20

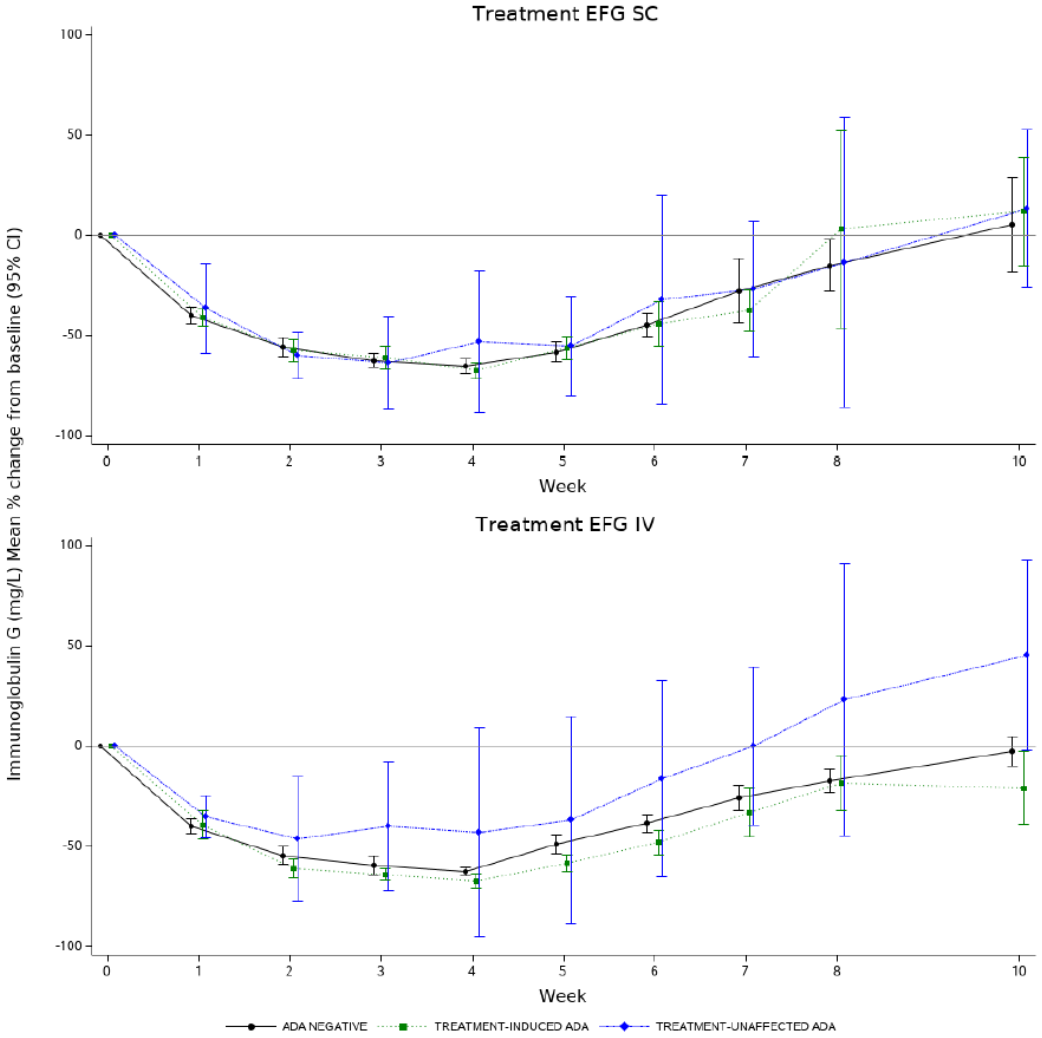
The observed incidence of ADA against rHuPH20 was 5.5% (3 of 55) in the efgartigimod PH20 SC arm of Study 2001. NAb against rHuPH20 was not detected, but the incidence of NAb is not informative due to insufficient sensitivity of the NAb assay (refer to OBP review). The Applicant observed no apparent impact of NAb against rHuPH20 on the PK, PD, or efficacy of efgartigimod PH20 SC. The review team believes that the ADA and NAb against rHuPH20 are not expected to affect the interpretation of clinical efficacy results, since rHuPH20 is not the active ingredient and is not measurable in the systemic circulation at clinically relevant doses. The review team recommends not to include the labeling descriptions about ADA or NAb against rHuPH20.

Figure 18. Mean (± SD) Efgartigimod Serum Concentrations by ADA Subject Classification in ARGX-113-2001



Source: Applicant's integrated summary of immunogenicity, page 64, Figure 12. Notes: In the efgartigimod IV arm, PK was sampled predose and postdose (at the end of the infusion). In the efgartigimod PH20 SC arm, no postdose PK samples were collected. In both arms, PK was sampled on days 1, 8, 15, 22, 29, 36, 43, 50, 57, and 71. ADA categories with at least 2 data points are represented.
Abbreviations: ADA, antidrug antibodies; EFG, efgartigimod; IV, intravenous; SD, standard deviation

Figure 19. Mean Percent Change From Baseline in Total IgG Levels (95% Confidence Interval) by Subject Classification of ADA Against Efgartigimod in ARGX-113-2001



Source: Applicant's integrated summary of immunogenicity, page 66, Figure 13. Notes: PD (total IgG concentrations) samples are taken on days 1, 8, 15, 22, 29, 36, 43, 50, 57, and 71.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval; EFG, efgartigimod; IgG, immunoglobulin gamma; IV, intravenous; SC, subcutaneous

Subjects who received rescue therapy with IVIg or plasmapheresis therapy (five subjects in the efgartigimod PH20 SC arm; one subject in the efgartigimod IV arm) showed elevated IgG levels and were included in this analysis. This may further explain the variability in total IgG reductions seen as of week 7. ADA categories with at least two data points are represented.

14.5. Pharmacometrics Assessment

14.5.1. Applicant's Analysis

The reduction in AChR-Ab following treatment with efgartigimod IV and efgartigimod rHuPH20 SC were evaluated in Study 2001 (Table 16). The percent change from baseline in AChR-Ab levels was analyzed using ANCOVA with treatment as a factor and AChR-Ab levels

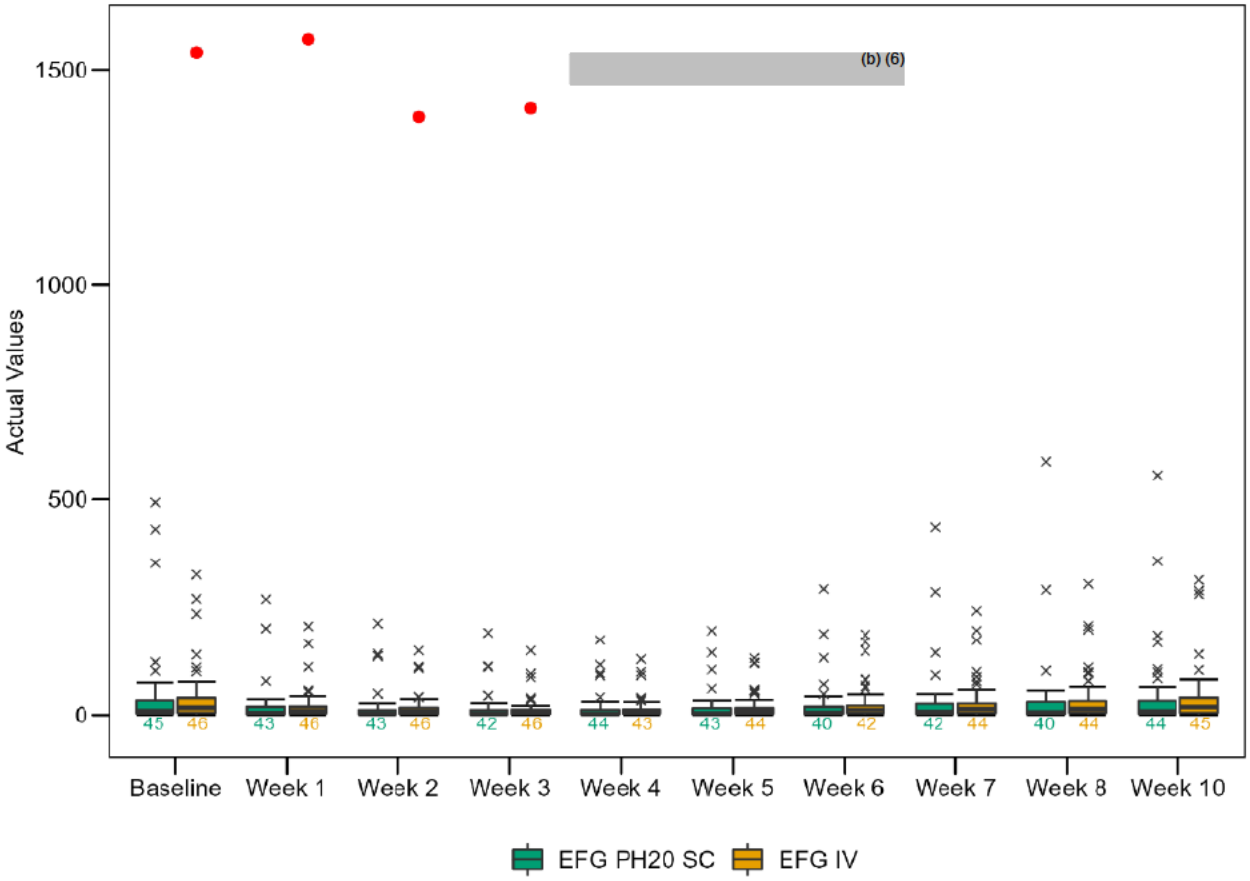
at baseline as a covariate. AChR-Ab percent reduction at day 29 in subjects with gMG who received efgartigimod PH20 SC 1008 mg was compared to that in subjects who received efgartigimod IV 10 mg/kg after one treatment cycle of 4-weekly administrations.

The Applicant calculated the geometric mean ratio (GMR) and 90% confidence interval (CI) of the percent change from baseline in AChR-Ab level at day 29 (Table 16), which was 1.05 (0.93-1.18) and within the range of 0.8-1.25, a criterion that is commonly used in PK bioequivalence as well as biosimilar programs to evaluate PD comparability. The results suggested that the percent change from baseline in AChR-Ab level at day 29 was comparable between the IV and SC treatments. Similarly, other PD metrics such as the E_{max}, $AUEC_{0-4w}$ and $AUEC_{0-10w}$ also showed comparable percent reduction in AChR-Ab as shown in Table 16.

The Applicant also conducted a noninferiority (NI) evaluation based on a percent reduction from baseline in AChR-Ab levels at day 29 (week 4). The confidence limits for difference in percent change are based on a two-sample t-test using SATTERTHWAITE's approximation. The least-squares mean estimate of the percent change from baseline in AChR-Ab level at day 29 was −62.2% (95% CI: −65.64 to −58.75) in the efgartigimod PH20 SC arm and −59.7% (95% CI: −63.20 to −56.15) in the efgartigimod IV arm. The corresponding least-squares mean difference in the percent change from baseline in AChR-Ab levels at day 29 between the 2 arms (efgartigimod PH20 SC versus efgartigimod IV) was −2.5% (95% CI: −7.45 to 2.41). The upper limit of the CI (2.41%) was below the protocol-specified NI margin of 10%, which supports that the efgartigimod PH20 SC was NI to efgartigimod IV based on AChR-Ab.

The reviewer noted a considerable imbalance in AChR-Ab baseline values between the IV and SC arms in Study ARGX-113-2001. An IR was sent on January 9, 2023, to request the analyses to evaluate potential impact of the imbalance on the conclusion of bridging with AChR-Ab as the PD biomarker. The Applicant's response dated January 17, 2023, stated that the imbalance in AChR-Ab baseline values between the IV and SC arms in ARGX-113-2001 was driven by an observation from a single subject in the IV treatment arm ((b) (6)), who had an extremely high AChR-Ab value at baseline (1540 nmol/L). High AChR-Ab values in this subject were also seen at following visits (Figure 20). For this specific subject, no PD data were available after week 3, and this subject discontinued from the study 44 days after the administration of efgartigimod IV. Results from subject (b) (6) were not included due to missing data at week 4.

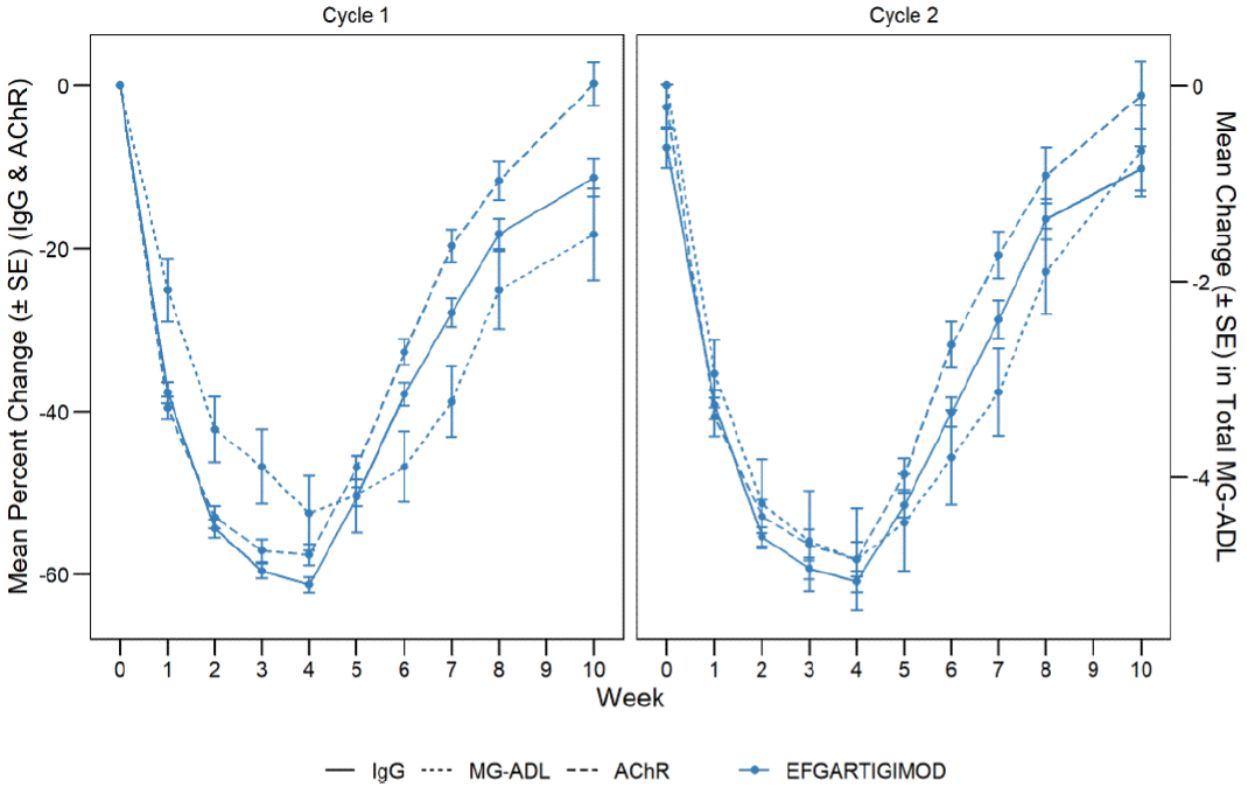
Figure 20. AChR-Ab Levels (nmol/L) Over Time for AChR-Ab Seropositive Subjects With gMG in ARGX-113-2001



Source: Applicant's IR response submitted on January 17, 2023, page 19, Figure 6. Notes: The whiskers represent 1.5 times the interquartile range. X represents values outside of the range covered by the whiskers. Red dots represent data from subject (b) (6) .
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; gMG, generalized myasthenia gravis; IV, intravenous

A decrease in AChR-Ab was associated with a clinical response in AChR-Ab positive subjects, as measured by the change from baseline in MG-ADL total score, as observed in Study 1704 (Figure 21). The reduction of AChR-Ab followed the pattern of reduction of total IgG (Figure 21). Please also refer to Figure 5 and Figure 6(b) in BLA 761195 Integrated Review Section 6.3.1 for the changes of MG-ADL Total Score, AChR-Ab, and total IgG from baseline in AChR-Ab seropositive subjects following treatment with efgartigimod.

Figure 21. Change in MG-ADL Total Score and Percent Change in Levels of Total IgG and AChR-Ab by Cycle in AChR-Ab Seropositive Population



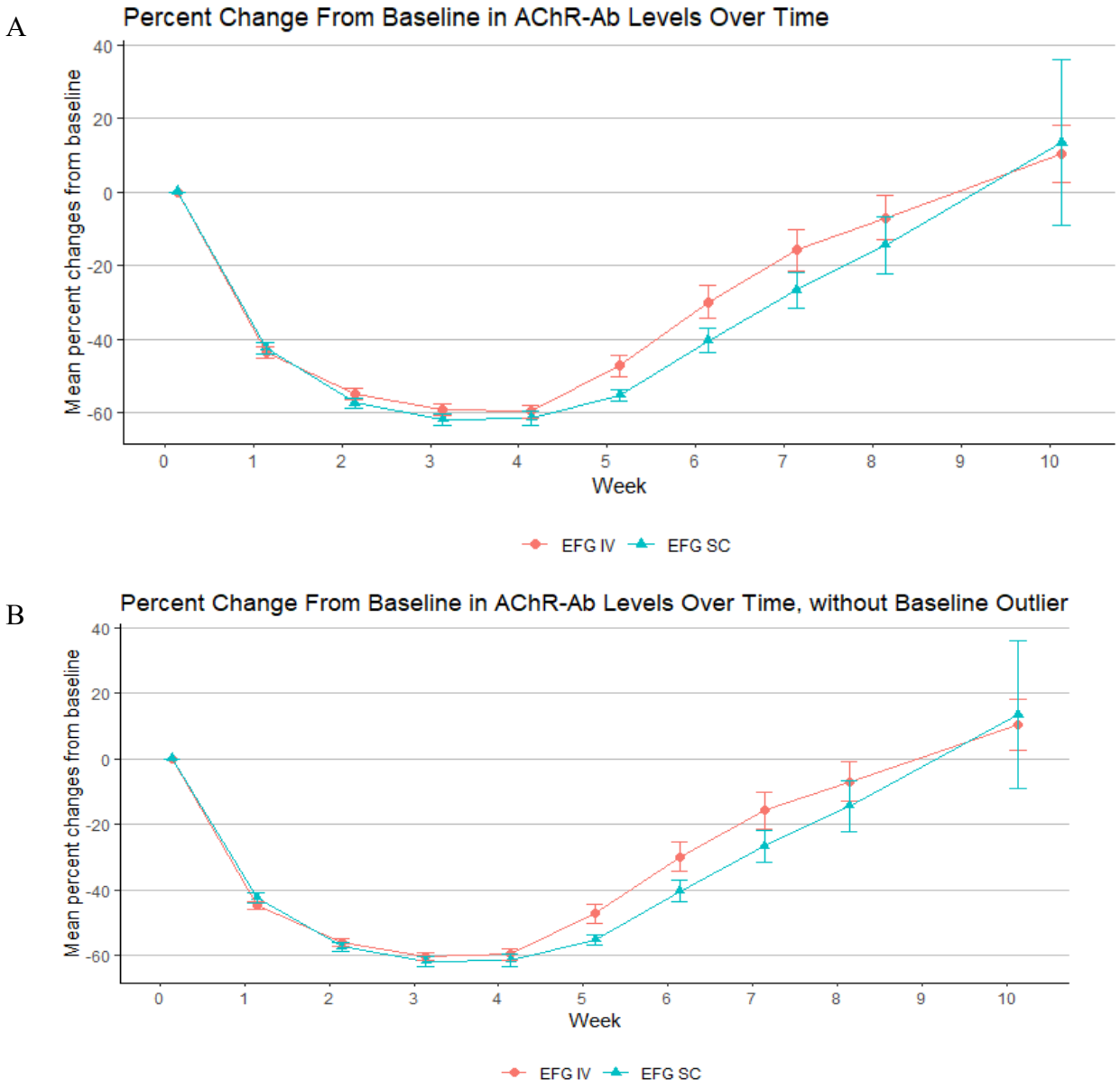
Source: Applicant's BLA 761195 (efgartigimod IV) summary of clinical pharmacology studies, page 35, Figure 11.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living

14.5.2. Reviewer's Analysis

The reviewer conducted independent analysis with data in Study 2001 to calculate the geometric mean ratio (GMR) (90% CI) for percent change from baseline in AChR-Ab level at day 29 and the AUEC at week 0 to 4 and has confirmed that these PD metrics were comparable between the IV and SC treatments, with the 90% CI within the range of 80% to 125%.

The percent reduction in AChR-Ab level at day 29 remains unchanged after removing Subject [redacted] (b) (6) who had a high baseline value (Figure 22). Thus, this imbalance of baseline had no impact on the conclusion of bridging with AChR-Ab as a PD marker.

Figure 22. Percent Change From Baseline in AChR-Ab Levels Over Time in the AChR-Ab Seropositive Population With or Without the Outlier



Source: Reviewer's Analysis
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; EFG, efgartigimod; IV, intravenous; SC, subcutaneous

The reviewer also conducted sensitivity analysis for the percent change in AChR-Ab on day 29 to evaluate the impact of (1) the six subjects who had missing doses; and (2) the samples with actual value lower than the lower limit of quantification (LLQ) 0.256 ng/mL, but was imputed as 0.256 ng/mL. The results are summarized in Table 65, which suggest no impact on the conclusion of bridging based on AChR-Ab percent reduction.

Table 65. Percent Reduction of AChR-Ab on Day 29 Following SC Treatment in Study 2001

Variable	SC Mean (SE)	IV Mean (SE)	GMR (90% CI)
Original dataset	62.2 (1.76)	59.6 (1.74)	1.04 (1.17, 0.93)
Removing samples with imputed values (A)	62.1 (1.82)	60.3 (1.7)	1.03 (0.92, 1.16)
Removing samples with missing doses (B)	64.2 (1.27)	59.6 (1.74)	1.10 (1.01, 1.21)

A: without the subjects who had AChR-Ab less than LLOQ (0.256) at baseline or week 29 and was imputed as 0.256: (b) (6)

B: without the subjects with missing doses (received <4 injections: (b) (6)
)

Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; CI, confidence interval; GMR, geometric mean ratio; IV, intravenous; SC, subcutaneous

14.6. Pharmacogenetics

Not applicable.

15. Study Design

Not applicable.

16. Efficacy

Not applicable.

17. Clinical Safety

Not applicable.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

(b) (4)

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study ARGX-113-2001 (BLA 761304) conducted at Wielospecjalistyczna Poradnia Lekarska, Katowice, Poland. OSIS concluded that the data from the audited study is reliable.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out.

Office of Regulatory Affairs (ORA) investigator Brandy D. Brown inspected Wielospecjalistyczna Poradnia Lekarska, Katowice, Poland, from March 27-31, 2023. This was the first OSIS inspection of Wielospecjalistyczna Poradnia Lekarska under the BA/BE program.

The current inspection included auditing the following items:

- Source record documentation
- Informed consent procedures
- Protocol adherence & deviations
- Independent Ethics Committee (IEC) approvals
- Adverse event reporting and follow-up
- Monitoring
- Test article accountability, storage, and dispensing

- Facilities
- Study personnel training
- Subject sample collection & processing
- Randomization

At the conclusion of the inspection, investigator Brandy D. Brown did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

23. Labeling: Key Changes and Considerations

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 66). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 66. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	• Not applicable
1 INDICATIONS AND USAGE	• (b) (4) "adult patients who are anti-acetylcholine receptor (AChR) antibody positive", which aligns with the approved indication for Vyvgart intravenous (IV). (b) (4)
2 DOSAGE AND ADMINISTRATION	• A subsection, Important Dosage and Administration Instructions (2.2), was created according to recommendations in the Guidance for Industry, Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2023). • (b) (4)

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	• [redacted] "VYVGART HYTRULO is to be administered by a healthcare professional only." • [redacted]
4 CONTRAINDICATIONS	• No changes
5 WARNINGS AND PRECAUTIONS	• 5.1 Infections: Text from the approved Vyvgart IV PI regarding a higher frequency of efgartigimod alfa-fcab patients having below normal levels of white blood cell, lymphocyte, and neutrophil counts compared to placebo was added for consistency and completeness. • 5.2 Hypersensitivity Reactions: Revisions were made to clarify that rash, angioedema, and dyspnea were seen with both Vyvgart Hytrulo and Vyvgart IV, and that urticaria was also seen in patients treated with Vyvgart Hytrulo.
6 ADVERSE REACTIONS	• [redacted] the presentation of safety information was revised to include the text from the approved Vyvgart IV PI for Study 1 with a subsequent heading that containing notable Vyvgart Hytrulo additional adverse reactions (e.g., injection site reactions) from Study 2. • The immunogenicity information was relocated to subsection 12.6 (see discussion under Clinical

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	Pharmacology section of this table).
7 DRUG INTERACTIONS	• No changes
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	• 8.1 Pregnancy: The exposure comparisons for the animal data to the recommended human dose were revised to reflect that of the Vyvgart Hytrulo components and doses. (b) (4) [redacted] • 8.2: Lactation: The hyaluronidase component was added to the statement regarding lack of information pertaining to lactation. • 8.4 Pediatric Use: No changes • 8.5 Geriatric Use: No changes • 8.6 Renal Impairment: No substantial changes
9 DRUG ABUSE AND DEPENDENCE	• Not applicable
10 OVERDOSAGE	• Not applicable
12 CLINICAL PHARMACOLOGY	• 12.1 Mechanism of Action: No changes • 12.2 Pharmacodynamics: (b) (4) [redacted] information regarding the mean reduction in AChR-Ab levels, which is the biomarker that was used for the bridge from Vyvgart IV to Vyvgart Hytrulo. Text from the approved Vyvgart IV PI was also included for consistency. • 12.3 Pharmacokinetics: No substantial changes • 12.6 Immunogenicity: Information was relocated from the Adverse Reactions section to the Clinical Pharmacology section per recommendations in the Guidance for Industry, Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format (February 2022). Information regarding the number of patients in Study 2 who received efgartigimod alfa-fcab intravenously who developed anti-efgartigimod alfa antibodies and neutralizing anti-efgartigimod alfa antibodies was added. A notation about the assay limitations for neutralizing antibody detection was also added.
13 NONCLINICAL TOXICOLOGY	• (b) (4) [redacted]

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	[redacted] (b) (4)
14 CLINICAL STUDIES	• [redacted] (b) (4) With the bridge being established, the efficacy of Vyvgart Hytrulo is based on the results from the Vyvgart IV study (Study 1).
17 PATIENT COUNSELING INFORMATION	• [redacted] (b) (4)
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	• The Applicant proposed to state the strength of the efgartigimod alpha component as [redacted] (b) (4) mg. However, it was confirmed with the Applicant that investigators were instructed to administer 5.6 mL to subjects receiving Vyvgart Hytrulo in Study 2. With 180 mg of efgartigimod alpha per mL, the strength was revised to 1008 mg per 5.6 mL (i.e., per vial). • Additional information concerning the cell line and drug substance manufacturing was added to the Description section. • Statements to clarify that the drug product should only be stored at room temperature for a single period were added. To help mitigate medication errors based on improper storage, a statement was added recommending to document on the carton both the date the vial was removed from the refrigerator and the date the vial was returned to the refrigerator.

Source: Applicant proposed PI received September 20, 2022
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): gMG, generalized myasthenia gravis; PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information

- Container label
- Carton labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRS) were required and agreed upon with the Applicant:

4462-1

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

Draft Protocol Submission:	07/2023
Final Protocol Submission:	10/2023
Interim Reports:	
	03/2024 03/2025 03/2026 03/2027 03/2028 03/2029 03/2030 03/2031 03/2032 03/2033
Study Completion:	01/2033
Final Report Submission:	12/2033

4462-2

Perform a lactation study (milk only) in lactating women who have received therapeutic doses of efgartigimod alfa and hyaluronidase-qvfc using a validated assay to assess concentrations of efgartigimod alfa in breast milk and the effects on the breastfed infant as applicable.

Draft Protocol Submission:	04/2024
Final Protocol Submission:	11/2024
Study Completion:	04/2026

25. Financial Disclosure

Table 67. Covered Clinical Studies: ARGX-113-2001 and ARGX-113-2002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 48		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

○ References

Gilhus, NE, 2016, Myasthenia Gravis, N Engl J Med, 375(26):2570-2581.

Gilhus, NE, S Tzartos, A Evoli, J Palace, TM Burns, and J Verschuuren, 2019, Myasthenia gravis, Nat Rev Dis Primers, 5(1):30.

Jaretzki, A, 3rd, RJ Barohn, RM Ernstoff, HJ Kaminski, JC Keesey, AS Penn, and DB Sanders, 2000, Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Ann Thorac Surg, 70(1):327-334.

Koneczny, I and R Herbst, 2019, Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture, Cells, 8(7).

Muppidi, S, 2012, The myasthenia gravis--specific activities of daily living profile, Ann N Y Acad Sci, 1274:114-119.

Nicolle, MW, 2016, Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome, Continuum (Minneap Minn), 22(6, Muscle and Neuromuscular Junction Disorders):1978-2005.

Wang, Y, X Huan, K Jiao, Q Jiang, LY Goh, J Shi, Z Lv, J Xi, J Song, C Yan, J Lin, W Zhu, X Zhu, Z Zhou, R Xia, S Luo, and C Zhao, 2022, Plasma exchange versus intravenous immunoglobulin in AChR subtype myasthenic crisis: A prospective cohort study, Clin Immunol, 241:109058.

26. Review Team

Table 68. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Michael Matthews / Heather Bullock (CPMS)
Nonclinical reviewer	Ed Fisher
Nonclinical team leader	Lois Freed
OCP reviewer(s)	Yifei Zhang, Xiulian Du
OCP team leader(s)	Bilal AbuAsal, Yow-Ming Wang
Clinical reviewer	Rainer Paine
Clinical team leader	Laura Jawidzik
Biometrics reviewer	None
Biometrics team leader	None
Cross-disciplinary team leader	Laura Jawidzik
Division director (pharm/tox)	Lois Freed
Division director (OCP)	Bilal AbuAsal
Division director (OB)	N/A
Division director (clinical)	Emily Freilich (acting)
Designated signatory authority	Emily Freilich

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 69. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Chana Fuchs (Application Technical Lead) Anh-Thy Ly (Regulatory Business Project Manager) Hao Kiet Phan (Drug Substance) Shen Luo (Drug Product) Frederick Mills (immunogenicity) Scott Dallas (Labeling) Vicky Borders-Hemphill (Labeling) Zhong Li (OPMA facility TL) Maxwell Van Tassell (TL micro DS and DP)
Microbiology	Bo Chi (DS micro and facility) Wayne Seifert (DP micro and facility)
OPDP	Sapna Shah
OSI	None
OSE/DEPI	Kira Leishear White Silvia Perez-Vilar
OSE/DMEPA	Colleen Little Ebony Whaley
OSE/DRISK	Jacqueline Sheppard
OSIS	Makini Cobourne-Duval Douglas Pham Seongeun (Julia) Cho
Safety	Sally Jo Yasuda
Pharmacometrics	Atul Bhattaram
Associate Director for Labeling	Tracy Peters
DPV	Allan Brinker David Croteau

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

26.1. Reviewer Signatures

See next page.

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Reviewer	Rainer Paine ON DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 2, 3, 4, 6, 7, 8, 10, 22, 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Rainer W. Paine -S Digitally signed by Rainer W. Paine -S Date: 2023.06.20 09:34:36 -04'00'					
Clinical Cross-Disciplinary Team Lead	Laura Jawidzik ON DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: all	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Laura A. Jawidzik -S Digitally signed by Laura A. Jawidzik -S Date: 2023.06.20 11:04:53 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Division Director (Acting)	Emily Freilich ON DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Emily R. Freilich -S Digitally signed by Emily R. Freilich -S Date: 2023.06.20 07:56:36 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/Toxicology Primary Reviewer	Ed Fisher ON DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: J Edward Fisher -S Digitally signed by J Edward Fisher -S Date: 2023.06.12 11:55:04 -04'00'					
Pharmacology/Toxicology Team Leader	Lois Freed ON DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Lois M. Freed -S Digitally signed by Lois M. Freed -S Date: 2023.06.12 12:05:15 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology/Pharmacometrics Primary Reviewer	Yifei Zhang OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3, 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yifei Zhang -S Digitally signed by Yifei Zhang -S Date: 2023.06.12 16:46:48 -04'00'					
Clinical Pharmacology Team Leader	Bilal AbuAsal OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3, 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Bilal Abu Asal -S Digitally signed by Bilal Abu Asal -S Date: 2023.06.12 16:30:45 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology/Pharmacometrics Team Leader	Atul Bhattaram OCP DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3, 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Venkatesh A. Bhattaram -S Digitally signed by Venkatesh A. Bhattaram -S Date: 2023.06.12 16:40:59 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Associate Director	Yow-Ming Wang OCP IO	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.3.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yow Ming C. Wang -S Digitally signed by Yow Ming C. Wang -S Date: 2023.06.19 11:23:40 -04'00'					
Clinical Pharmacology Reviewer	Xiulian Du OCP IO	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.3.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Xiulian Du -S Digitally signed by Xiulian Du -S Date: 2023.06.19 11:02:04 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Associate Director for Labeling	Tracy Peters ON DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Tracy Peters, PharmD					
Product Quality Team Leader	Chana Fuchs OBP DBRRIV	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ x-Yes ☐ NO
Signature/date/time stamp: Chana Fuchs -S Digitally signed by Chana Fuchs -S Date: 2023.06.14 15:18:57 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Regulatory Project Management Primary Reviewer	Michael Matthews ORO DRON	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Michael Matthews -S Digitally signed by Michael Matthews -S Date: 2023.06.12 11:05:58 -04'00'					
Regulatory Project Management CPMS	Heather Bullock ORO DRON	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Heather M. Bullock -S Digitally signed by Heather M. Bullock -S Date: 2023.06.12 11:29:14 -04'00'					

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
06/20/2023 01:18:25 PM