CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761195Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	761195
Priority or standard	Standard
Submit date(s)	12/17/2020
Received date(s)	12/17/2020
PDUFA goal date	12/17/2021
Division/office	Division of Neurology I (DNI)
Review completion date	12/17/2021
Established/proper name	Vyvgart (efgartigimod alfa – fcab)
(Proposed) proprietary name	Vyvgart
Pharmacologic class	Neonatal FcRn blocker
Code name	ARGX-113
Applicant	argenx BV
Dosage form(s)/formulation(s)	20 mL single-dose vial contains 400 mg efgartigimod alfa at a concentration of 20 mg/mL / formulated in water for injection contains 25mM sodium phosphate, 100mM sodium chloride, 150mM L-arginine hydrochloride, and 0.02% polysorbate 80.
Dosing regimen	10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks.
Applicant proposed indication(s)/ population(s)	For the treatment of adults with generalized myasthenia gravis
Proposed SNOMED indication	91637004 Myasthenia Gravis
Regulatory action	Approval
Approved dosage (if applicable)	10 mg/kg
Approved indication(s)/ population(s) (if applicable)	For the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive
Approved SNOMED term for indication (if applicable)	91637004 Myasthenia Gravis

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Glossary

AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	acetylcholine receptor-antibody
AChR-MG	acetylcholine receptor-antibody positive myasthenia gravis
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BILI	bilirubin
BLA	biologics license application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
C1B	baseline of the first cycle
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMI	clinically meaningful improvement
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DVRPA	Division of Vaccines and Related Product Applications
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
E_{max}	maximum effect
FcRn	Fc receptor
FDA	U.S. Food and Drug Administration
FVC	forced vital capacity
gMG	generalized myasthenia gravis
HDL	high-density lipoprotein
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
ITC	intertreatment cycle
IV	intravenous
IVIG	intravenous immunoglobulin
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LRP4	low-density lipoprotein receptor-related protein 4

Reference ID: 4907061

MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Specific Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MuSK	muscle specific kinase
NSID	nonsteroidal immunosuppressive drug
OBP	Office of Biotechnology Products
OR	odds ratio
OVRR	Office of Vaccine Research and Review
PD	pharmacodynamic
PK	pharmacokinetic
q7d	every 7 days
QMG	Quantitative Myasthenia Gravis
QTcF	QT interval using Fridericia's Correction
SAD	single ascending dose
SAE	serious adverse event
SEB	screening and baseline
SMQ	Standardised MedDRA Query
SOC	system organ class
TB	tuberculosis
TC	treatment cycle
TEAE	treatment-emergent adverse event
UTI	urinary tract infection
V	volume of peripheral compartment

I. Executive Summary

1. Summary of Regulatory Action

Argenx BV submitted a biologics license application (BLA) 761195 for efgartigimod. Efgartigimod is a first-in-class, neonatal Fc receptor blocker for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

BLA 761195 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 results from a single adequate and well-controlled study (Study 1704), with support from pharmacodynamic/mechanistic data, that provide substantial evidence of effectiveness of efgartigimod for the indication and supports approval for the treatment of adults with gMG who are seropositive for the AChR antibody. Study 1704 was a well-designed multicenter study that provided reliable and highly statistically significant ($p<0.0001$) evidence of an important patient-reported impact and clinical benefit on daily function on an acceptable primary outcome (the percentage of Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) responders). Efficacy was further supported by a highly statistically significant ($p<0.0001$) secondary endpoint result using a validated direct physician assessment of motor function in gMG subjects (the percentage of Quantitative Myasthenia Gravis (QMG) responders). Supplementary analyses supported the primary and secondary results. Overall, the highly persuasive results on a clinically meaningful endpoint, with support on the secondary endpoint of QMG and multiple supplementary analyses, make reliance on a single efficacy study in this rare disease, with confirmatory evidence from relevant and supportive pharmacodynamic/mechanistic data, appropriate to support approval.

Although Study 1704 enrolled subjects with gMG who were seropositive for AChR antibodies and seronegative for AChR antibodies, the primary endpoint evaluated the effect of efgartigimod only in those who were seropositive for the AChR antibody. (b) (4)

Thus, the product will be indicated in the AChR antibody positive population.

The available safety data show that risks of efgartigimod are acceptable for its intended use. I concur that identified risks can be mitigated through labeling and further evaluated during routine and enhanced pharmacovigilance. 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 the 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, 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 pyridostigmine bromide, which is FDA-approved for MG. Treatments such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, plasmapheresis, and intravenous immunoglobulin are used off-label. Thymectomy is also a treatment option for some patients. Eculizumab (Soliris) is a C5 inhibitor that is FDA-approved for adults with generalized myasthenia gravis who are AChR positive, although it carries a boxed warning for serious meningococcal infections and has an associated Risk Evaluation and Mitigation Strategy (REMS). Eculizumab is indicated for treatment of AChR-MG, but is not indicated for MuSK antibody positive or LRP4 antibody positive patients.	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 MG patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments.
Benefit	• The efficacy of efgartigimod was evaluated in Study 1704, a 28-week double-blind placebo-controlled multicenter trial that enrolled 167 individuals with gMG. Subjects were randomized 1:1 in a blinded fashion to a 4-week treatment cycle of once weekly infusions of either efgartimod 10 mg/kg or placebo with a 24-week follow-up period. Efficacy was assessed 8 weeks after the initiation of treatment. • The primary efficacy endpoint was the percentage of Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) responders during cycle 1 in the AChR-Ab seropositive population. A subject was considered an MG-ADL responder if there was a ≥2-point reduction in the MG-ADL total score compared to baseline that was maintained for four consecutive weeks (i.e., five consecutive visits total), with the first reduction occurring no later than 1 week after the last infusion of the product in cycle 1. • The secondary efficacy endpoint was the percentage of Quantitative Myasthenia Gravis (QMG) responders during cycle 1 in the AChR-Ab seropostive population. A subject was considered a QMG responder if there was a ≥3-point reduction in the MG-ADL total score compared to baseline that was maintained for four consecutive weeks (i.e., five consecutive visits total), with the first reduction occurring no later than 1 week after the last infusion of the product in cycle 1. • In Study 1704, for subjects with AChR-MG, there was a higher percentage of MG-ADL responders in the efgartigimod group (68%) compared to the placebo control group (30%; p<0.0001) after 8 weeks.	The 28-week placebo-controlled study of efgartigimod provided reliable and statistically persuasive evidence that efgartigimod can help AChR-MG subjects achieve a clinically meaningful improvement in the symptoms of the disease that affect their activities of daily living. Efgartigimod binds to Fc receptor (FcRn), resulting in a reduction of circulating immunoglobulin G (IgG), including IgG autoantibodies. This mechanism of action is not specific to a particular autoantibody. It is therefore possible that efgartigimod may have an effect not only on myasthenia gravis caused by anti-AChR antibody but also on MG caused by other autoantibodies. When tested by a specialized cell-based immunofluorescence assay, up to one-half of subjects with seronegative myasthenia gravis by standard assays have clustered AChR antibodies (also called low-affinity AChR antibodies). (b) (4) [redacted]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• For subjects with AChR-MG, there was also a higher percentage of QMG responders in the efgartigimod group (63%) compared to the placebo control group (14%; p<0.0001) after 8 weeks. • In the overall population, the percentage of MG-ADL responders was higher in the efgartigimod group (68%) than in the placebo group (38%; p<0.0001). (b) (4) The treatment effect in the overall population was driven by the effect in the AChR population.	
Risk and risk management	• The safety database included 246 subjects exposed to at least one dose of efgartigimod. Of the 246 subjects, 57 with generalized myasthenia gravis (gMG) received at least 7 cycles of efgartigimod and were treated for at least 6 months, and 48 were treated over 12 months at the proposed dose at the time of the 90-Day Safety Update. The minimum time to initiation of another treatment cycle, defined by the protocol in the open-label extension study, was 50 days. Safety Concerns • There were five deaths in the database. All of the deaths occurred in the open-label extension study. Two of the five deaths (septic shock and myasthenia gravis crisis) occurred in the setting of infection, and a role for efgartigimod could not be ruled out given that infections were among the most frequently reported adverse events (AEs) in the placebo-controlled studies. In both cases, subjects had additional potential contributory factors for the events related to infection. In the remaining three deaths, subjects had underlying risk factors and the deaths were not attributable to treatment with efgartigimod. • The most common TEAEs in the phase 3 controlled trial (at least 5% in the efgartigimod arm and 1% greater than placebo) were urinary tract infection (UTI) (up to 10%), myalgia (up to 6%), paresthesia (up to 7%), respiratory tract infection (up to 33%), and headache (up to 32%).	The safety database is adequate in terms of size and dosing given that generalized myasthenia gravis is a rare disease. Approval should be accompanied by labeling language to alert the prescriber to the risks of infection and hypersensitivity reactions. The safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established. There was an imbalance between efgartigimod and placebo in AEs related to infection, including events related to respiratory tract infection and UTI. Uncertainty exists in whether outcomes of infections would be more serious in an unmonitored outpatient setting or in patients with greater risk for immunosuppression. A Warning and Precautions statement for infections would highlight the need for awareness of the potential for infections and may mitigate the risk for serious outcomes. Enhanced pharmacovigilance for serious adverse events related to infection is recommended. Potentially serious hypersensitivity reactions, including angioedema, have been reported. A

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Infections occurred in 46% of subjects who received efgartigimod compared to 37% of subjects who received placebo in the phase 3 controlled trial. There was no excess of SAEs related to infection in the efgartigimod arm compared to placebo in the phase 3 controlled trial. Treatment with efgartigimod was associated with reductions in IgG levels and with an increased frequency of low leukocytes (up to 12%), low lymphocytes (up to 28%), and low neutrophils (up to 13%) in efgartigimod-treated subjects as compared to placebo-treated subjects. • Hypersensitivity reactions, including angioedema, dyspnea, and rash were observed in efgartigimod-treated subjects. All cases of angioedema and most cases of rash were mild. No cases of hypersensitivity-related reactions were serious or led to treatment discontinuation. Other uncertainties • The risk for serious outcomes of infections in the postmarketing period, when patients are likely to be observed less frequently than in clinical trials, is unknown. • Potential for fetal harm: the risk of adverse outcomes in pregnancy has not been characterized. • Given the short duration of the clinical trials, the risk of malignancy has not been characterized. • Given the small number of hepatitis B carriers in the clinical trials and absence of subjects with a history of latent tuberculosis, the risk of reactivation of hepatitis B and latent tuberculosis with efgartigimod is unknown.	Warnings and Precautions statement would alert patients and providers to this risk. Because efgartigimod is associated with infection and reductions in IgG levels, a Warnings and Precautions statement in labeling would help alert providers that the safety of administration of live or live-attenuated vaccines, and that the response to immunization with any vaccine is unknown. Patients should be vaccinated with all age-appropriate vaccines according to immunization guidelines before initiating therapy with efgartigimod. (b) (4) Because the risk of adverse outcomes in pregnancy has not been characterized, and because efgartigimod will be used in women of childbearing potential, a pregnancy outcomes study is recommended as a postmarketing requirement. Because the risk of malignancy and reactivation of hepatitis B and latent tuberculosis has not been characterized, enhanced pharmacovigilance for malignancy and reactivation of hepatitis B and latent tuberculosis is recommended.

Note: For this application, the group identified as AChR seronegative included six subjects who were positive for the MuSK antibody. Other potential autoantibodies were not measured.

2.2. Conclusions Regarding Benefit-Risk

MG 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 remains because not all MG patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Efgartigimod is a first-in-class, neonatal Fc receptor blocker being developed for the treatment of adults with generalized myasthenia gravis (gMG), which is proposed to work by reducing circulating IgG.

The Applicant has demonstrated the efficacy of efgartigimod for the treatment of gMG in patients with AChR antibodies in Study 1704, a 28-week double-blind placebo-controlled multicenter trial that enrolled 167 individuals with gMG who were on stable background therapy. Subjects received a 4-week treatment cycle of once weekly infusions of either efgartigimod 10 mg/kg or placebo, with efficacy assessed 8 weeks after the initiation of treatment. Subjects were followed for a 28-week period to assess the need for retreatment. Efgartigimod was superior to placebo on the primary endpoint and key secondary endpoint. A statistically significantly higher percentage of MG-ADL responders was observed in the efgartigimod group (67.7%) compared to the placebo group (29.7%) during the first cycle of treatment in the AChR antibody seropositive population ($p<0.0001$). Efficacy was further supported by a statistically significant higher percentage of QMG responders in the efgartigimod group (63%) compared to the placebo control group (14%; $p<0.0001$) after 8 weeks. The study was an adequate and well-controlled multicenter study that provided reliable and statistically strong evidence that efgartigimod can help adult MG patients who are seropositive for the AChR antibody achieve a clinically meaningful improvement in the symptoms of the disease that affect their activities of daily living.

(b) (4) The study enrolled subjects with gMG who were seropositive for AChR antibodies (77 %) and those who were seronegative for AChR antibodies (subjects with antibodies other than AChR or no detectable known autoantibodies) (23%). The primary endpoint of the study evaluated the effect of efgartigimod on AChR-MG. The overall population (combined AChR seropositive and AChR seronegative) achieved statistical significance; however, the entire effect in the overall population was driven by the AChR-MG group. (b) (4)

The efficacy results from Study 1704 support the approval of efgartigimod for the treatment of gMG in adult patients who are anti-AChR antibody positive. Study 1704 was an adequate and well-controlled study that demonstrated highly statistically significant treatment effects of efgartigimod on the study's primary efficacy endpoint, MG-ADL responder. The results were robust to any reasonable sensitivity analysis. The study was large (given the size of the patient population) and multicenter; no single study site provided an unusually large fraction of the patients, and no single investigative site was disproportionately responsible for the observed treatment effect. The primary finding was supported by the secondary endpoint, QMG, with rigorous control of the type-I

error rate. The distinct treatment effects on the MG-ADL and the QMG confirm that the observed treatment differences were highly clinically meaningful. Results were generalizable across important subsets based on demographic and baseline disease characteristics. Additionally, pharmacodynamic/mechanistic data relevant to the pathophysiology of the disease, reduction in total IgG and AChR antibodies, provide confirmatory evidence to support approval. Therefore, the study is capable of serving as a single study with confirmatory evidence that provides substantial evidence of effectiveness of efgartigimod in patients with gMG who are AChR antibody positive.The safety database for efgartigimod was adequate for the intended population and proposed dosing regimen. Overall, the safety experience with efgartigimod supports an acceptable risk/benefit profile. Any safety findings can be adequately addressed through labeling and through routine and enhanced pharmacovigilance. Warnings and precautions include infections, hypersensitivity reactions, and vaccination-related concerns. Common adverse reactions associated with treatment include respiratory tract infections, UTIs, myalgia, headaches, and hypo/hyperesthesia. Enhanced pharmacovigilance will be requested for malignancies, serious adverse events related to infections, and reactivation of hepatitis B and latent tuberculosis. A pregnancy outcomes study will be a postmarketing requirement.

Based upon the review of all available efficacy and safety data, the benefits of efgartigimod clearly outweigh the risks for the treatment of adult patients with gMG who are AChR antibody positive. The availability of efgartigimod will provide a new and effective treatment option for AChR-MG.

II. Interdisciplinary Assessment

3. Introduction

Efgartigimod (Vyvgart) is an intravenously administered human immunoglobulin G1 (IgG1) antibody fragment that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG, including IgG autoantibodies. The Applicant's proposed indication for efgartigimod is the treatment of adult patients with generalized myasthenia gravis (gMG). The proposed dose of efgartigimod is 10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks.

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. Approximately 85% of patients with MG have autoantibodies against the acetylcholine receptor (AChR). Several other autoantibodies have been identified as well, such and anti-muscle specific kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4). Myasthenia gravis with MuSK antibodies accounts for 1 to 10% of cases, while LRP4 antibodies are present in 1 to 3% of all patients with myasthenia gravis (Gilhus 2016). A small percentage of patients have no detectable autoantibodies. Patients with MG develop weakness in the skeletal muscles that worsens after periods of activity and improves after periods of rest. Life-threatening respiratory failure (myasthenic crisis) occurs in 15 to 20% of patients and requires immediate emergency medical care.

U.S. Food and Drug Administration (FDA)-approved treatments include anticholinesterase medications, such as pyridostigmine bromide and eculizumab. 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.

The pivotal trial, Study ARGX-113-1704 (referred to in the review as Study 1704), was a phase 3, multinational, randomized, double-blind, placebo-controlled study of efgartigimod in 167 adult subjects (84 efgartigimod, 83 placebo) with generalized myasthenia gravis. The total study duration was up to 28 weeks and included a 2-week screening period and an initial 8-week treatment cycle, which was followed by an intertreatment cycle of variable length depending on the subject's clinical response to efgartigimod.

The review team identified two key review issues that had a significant impact on the overall review of efgartigimod and the product labeling.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

(b) (4)

3.1.1.2. Length of Treatment Cycles and the Time Between Treatment Cycles

- Determine the minimum length of time between treatment cycles of efgartigimod that is supported by the available efficacy and safety data. The proposed prescribing information states that the physician should "Re-treat patients with treatment cycles of weekly infusions for 4 weeks according to clinical evaluation."

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Infections

3.1.2.2. Hypoalbuminemia

3.1.2.3. Dyslipidemia

3.1.2.4. Hypersensitivity Reactions

3.1.2.5. AEs in the AChR-Ab Seronegative Population

3.1.2.6. Immunizations

3.2. Approach to the Review

The studies submitted to support the safety and efficacy of efgartigimod are summarized below (Table 3). This BLA submission includes the pivotal phase 3 randomized, double-blinded placebo-controlled Study 1704, as well as data from an exploratory phase 2 randomized, double-blinded placebo-controlled study ARGX-113-1602 (Study 1602). Additional supportive safety data were also provided from the ongoing open-label extension Study ARGX-113-1705 (Study 1705), including data from the 90-Day Safety Update. These three studies were conducted in adults with gMG.

An efficacy determination was made by evaluating the results from the phase 3 placebo-controlled Study 1704 in adult subjects with gMG. Confirmation of the efficacy analyses was provided by the biometrics reviewer for this application. The safety assessment was based on the Applicant's reports and clinical reviewer analysis of the submitted data. The primary safety data were from Study 1704 with supportive data from Study 1602 and Study 1705.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for Efgartigimod

Trial Identifier	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	Number of Subjects	Number of Centers and Countries
ARGX-113-1602	gMG	Phase 2 randomized, double-blind, placebo-controlled	EFG or PBO 10 mg/kg IV on D1, D8, D15, D22 (1200 mg max dose) Treatment cycle: 4 infusions followed by 8-week follow-up period	1: Incidence of AEs and SAEs, vitals, ECG, labs 2: Change from baseline in MG-ADL, QMG, MGC, MGQoL15r	24 enrolled/ 23 completed	15 centers, 8 countries
ARGX-113-1704	gMG	Phase 3 randomized, double-blind, placebo-controlled multicenter	EFG or PBO 10 mg/kg IV weekly for four infusions Up to 28 wks Treatment cycle: 3-week treatment period, 5-week follow-up period, and an intertreatment cycle period where assessments are performed every 2 weeks to determine need for retreatment Minimum time to retreatment defined by protocol[1]: 68 days	1: % after first cycle with ≥2 point MG-ADL reduction for 4 weeks 2: % after first cycle with ≥3 point QMG decrease for 4 weeks	167 subjects randomized • AChR-Ab seropositive: 129 • AChR-Ab seronegative: 38 EFG arm: 84 PBO arm: 83	56 centers, 15 countries
ARGX-113-1705	gMG	Phase 3 long-term open-label, single-arm multicenter	EFG Cycles of EFG IV 10 mg/kg IV weekly for four infusions Part A: 1 year Part B: 2 years (max) Treatment cycle: 3-week treatment period and an intertreatment cycle period where assessments were performed every 30 days to determine need for retreatment Minimum time to retreatment defined by protocol[2]: 50 days	AEs, SAEs, vitals, ECG, labs. MG-ADL score change; QMG score change	135 subjects from Study 1704	38 centers, 14 countries

Source: Reviewer
[1] Based on the length of a treatment period, follow-up period, and the minimum intertreatment cycle period
[2] Based on the length of a treatment period and the minimum intertreatment cycle period for Part A.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; AE, adverse event; ECG, electrocardiogram; EFG, efgartigimod; gMG, generalized myasthenia gravis; IV, intravenous; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGQoL, Myasthenia Gravis Quality of Life; PBO, placebo; QMG, Quantitative Myasthenia Gravis; SAE, serious adverse event

4. Patient Experience Data

The following table lists the patient experience data relevant to this application.

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, 16.2.1
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6.2.1.1, 16.2.1
☐	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

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	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 and urine (as applicable in Study ARGX-113-1501 (Study 1501) concentrations of efgartigimod were determined by validated enzyme-linked immunosorbent assay (ELISA) methods. The ELISA method was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance.
Healthy subjects versus patients	Clinically relevant differences in PK are not expected between healthy subjects and patients
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	In the first treatment cycle following the fourth weekly dose of 10 mg/kg, mean (SD) values for C_{max} and C_{trough} were reported to be 253 (193) and 12.8 (6.25), respectively, from Study ARGX-113-1704 (Study 1704).
Range of effective dosage(s) or exposure	Only a single dose-level, 10 mg/kg infusion administered weekly for a total of four infusions (Q1W*4) per treatment cycle was studied in phase 2 (Study ARGX-113-1602 [Study 1602]) and phase 3 (Study 1704) studies.
Maximally tolerated dosage or exposure	The highest evaluated dose in humans was a single dose of 50 mg/kg in healthy subjects (n=4) in Study 1501.
Dosage proportionality	Efgartigimod exposures, C_{max} and AUC_{inf}, increased in an approximately dose-proportional manner when administered as a single dose in the range of 2 mg/kg to 50 mg/kg (Study 1501 part I) and slightly less than dose proportional manner following multiple doses in the range of 10 mg/kg to 25 mg/kg (Study 1501 part II).
Accumulation	Following four weekly doses of 10 mg/kg 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 by the fourth weekly dose, i.e., within end of the treatment of the cycle (Q1W*4).
Bridge between to-be-marketed and clinical trial formulations	Analytical comparability between the product used in phase 3 Study 1704 and the to-be-marketed product has been established. Therefore, no clinical PK-based bridging study is required.

Characteristic	Drug Information
	Absorption
Bioavailability	100% (Efgartigimod is administered intravenously as an infusion).
T_{max}	At the end of infusion (1 hour).
Food effect (fed/fasted) Geometric least square mean and 90% CI	Efgartigimod is administered intravenously as an infusion over 1 hour, 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	Bodyweight-based regimen was evaluated throughout the clinical development program for efgartigimod. In phase 2 Study 1602 and phase 3 Study 1704, subjects received four weekly doses of 10 mg/kg Q1W (one treatment cycle), and specifically subjects who weighed >120 kg received a fixed dose of 1200 mg Q1W*4.
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.
	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.

Characteristic	Drug Information
	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 1704, in up to 26 weeks of treatment, up to 20% (17/83) of subjects developed antibodies to efgartigimod and 7% (6/83) of subjects developed neutralizing antibodies.
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.

Abbreviations: AUC_{inf}, area under the curve over the entire time; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, plasma concentration reached prior to next dose; eGFR, estimated glomerular filtration rate; MW, molecular weight; PK, pharmacokinetic; SD, standard deviation

5.1. Nonclinical Assessment of Potential Effectiveness

FcRn is a multifunctional protein expressed primarily in epithelial cells and cells of myeloid lineage that binds the Fc portion of IgG and also binds albumin. Efgartigimod is a human IgG1-derived Fc fragment targeting the neonatal Fc receptor (FcRn). The product was designed to increase affinity for the FcRn at neutral and acidic pH. (b) (4)

When bound to the FcRn, efgartigimod blocks binding of IgG and inhibits the FcRn-mediated recycling of IgG. Inhibition of this recycling results in shorter half-life of plasma IgG and, thus, lower plasma IgG levels. When compared to "wild-type" Fc fragment binding, efgartigimod bound to human FcRn with significantly greater affinity than the wild-type Fc fragment at both neutral and acidic pH. In vitro binding and functional assays demonstrated that efgartigimod binds to FcRn of multiple species, and the affinity of the product is similar for human and monkey FcRn. with K_D values in the low nM range.

A series of in vivo studies were conducted to characterize the pharmacodynamic (PD) activity of efgartigimod (i.e., reduction in plasma IgG levels) and the potential for efficacy in animal models of myasthenia gravis. The expected reduction in plasma IgG was observed across studies in all species tested. Specificity was demonstrated in multiple studies, which demonstrated that levels of plasma IgM, IgA, and albumin were not affected after dosing with efgartigimod.

The potential efficacy of efgartigimod was investigated in multiple studies using passive transfer models of MG in rats. In these studies, a significant reduction in pathogenic IgG as well as total IgG was observed. Animals that were dosed with efgartigimod showed functional improvement (improved muscle strength and stabilization of grip strength) where control animals declined and, in some instances were euthanized early due to moribund condition. In a study using a passive transfer model for AChR-MG in Lewis rats, grip strength and clinical scoring were conducted at 72 hours post dose. Rapid reduction in IgG levels was observed (up to 50%) within 48 hours post dose, and efgartigimod dosed animals had lower clinical scores and increased grip strength relative to control animals.

In a study to evaluate the PD of efgartigimod in monkeys, when administered IV to cynomolgus monkeys at a dose of 20 mg/kg (single dose or repeated dosing every 4 days), IgG levels were reduced approximately 55% after both single and repeated dosing. With repeated dosing, the reduction in IgG was similar to that observed after a single dose but was of longer duration.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant conducted a phase 1 study ARGX-113-1501 (Study 1501) evaluating single doses of 0.2, 2, 10, 25, and 50 mg/kg; and multiple doses of 10 mg/kg every 4 days for 21 days, and 10 mg/kg and 25 mg/kg every 7 days for 22 days in adult healthy volunteers. Pharmacokinetic (PK) and pharmacodynamic (PD; total IgG reduction) data were collected. The Applicant noted

that no significant differences in the total IgG reduction were observed following single doses of 10, 25, or 50 mg/kg. Additionally, the Applicant noted that no significant differences in total IgG reduction were observed following 4 weekly infusions of 10 mg/kg or 25 mg/kg. Subsequently, the Applicant found that in subjects with gMG, a cycle of 4 weekly infusions of 10 mg/kg efgartigimod was considered safe and effective in phase 2 Study 1602. Based on the results from the phase 2 study, the Applicant conducted PK/PD/clinical response simulations of 500 clinical trials over a dose range of 5 to 20 mg/kg efgartigimod. The Applicant noted that these simulations indicated that:

(1) After four weekly infusions of efgartigimod intravenous (IV) 5, 10, or 20 mg/kg, the median (5th and 95th percentiles) maximal total IgG reductions were simulated to be 62% (49% to 75%), 71% (59% to 78%), and 77% (70% to 81%) after 5, 10, and 20 mg/kg, respectively. Although the median reduction increased, the intervals in reduction largely overlapped, especially at 10 and 20 mg/kg. A similar trend in increasing reduction in acetylcholine receptor antibody (AChR-Ab) levels with increased dose was observed.
(2) The projected response rates for a 2- or 3-point drop in Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) score were found to be similar across the dose levels 5, 10, and 20 mg/kg.

Based on the results from phase 1 and 2 studies and clinical trial simulations, the Applicant selected 10 mg/kg for phase 3 studies. They noted that dosing higher (i.e., 20 mg/kg) is not expected to result in an improved PD effect (i.e., further lowering of autoantibodies) and/or clinical benefit and may be associated with a less optimal risk/benefit ratio; and dosing lower (i.e., 5 mg/kg) is expected to result in lower PD effect and thus is likely to result in a less consistent and/or incomplete clinical response.

The Applicant noted that a 1-hour infusion duration was selected based on similarity in PK parameters after 4 weekly infusions of efgartigimod 10 mg/kg infused over 1 or 2 hours, and subject convenience. The Applicant also noted that the weekly interval for dosing was selected based on results from phase 1 Study 1501 in which the ranges of the maximal reduction of individual IgG levels were comparable between every 4-day and every 7-day dosing regimen (n=6 per dosing regimen). The clinical pharmacology team evaluated the proposed instructions by the Applicant for delayed or missed dosing and found it acceptable (Figure 17).

In summary, based on these considerations, the Applicant selected 10 mg/kg every 7 days for 4 weeks, each infused over 1 hour and administered in treatment cycles. Redosing was based on clinical evaluation (discussed in detail in Section 6.2.1.1).

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study 1704

6.2.1.1. Design

Overview and Objective

Study 1704 was a phase 3, multinational, randomized, double-blind, placebo-controlled study of efgartigimod in adult subjects with gMG.

The primary objective was to evaluate the efficacy of efgartigimod as assessed by the percentage of MG-ADL responders after the first treatment cycle (TC) in the AChR-Ab seropositive population.

The secondary objectives are listed below.

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

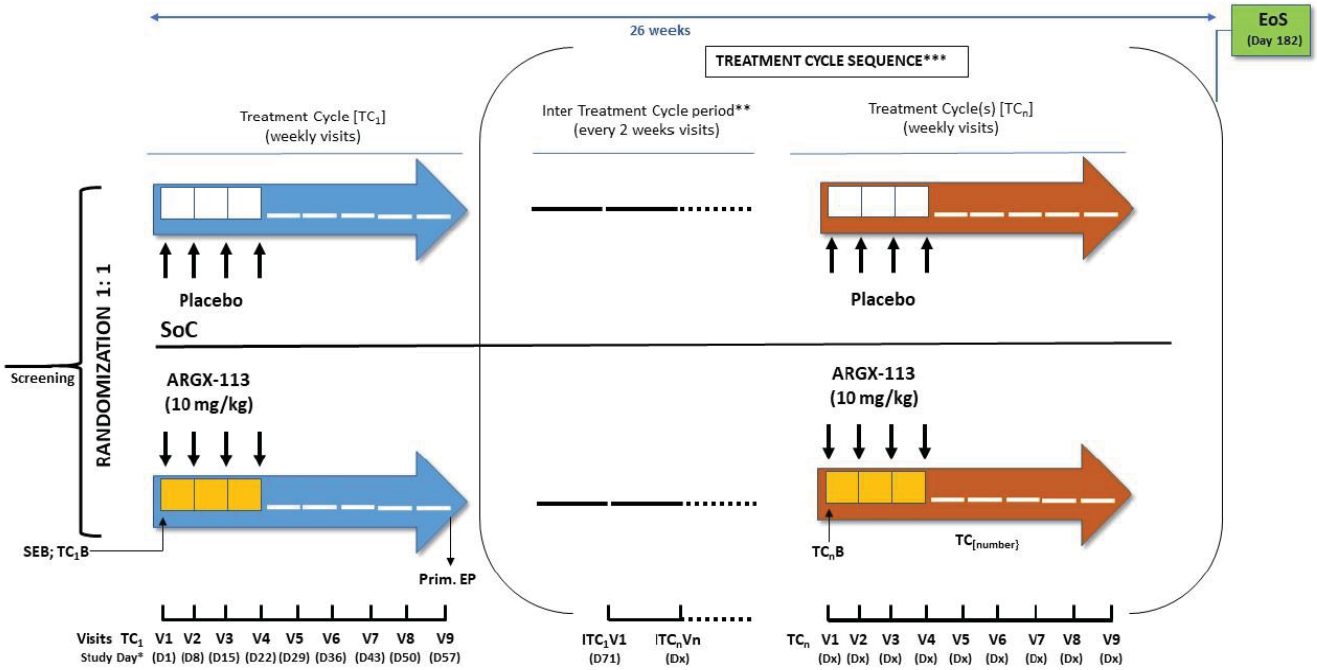
Basic Study Design

Study 1704 was a multicenter (56 study centers), multinational (15 countries), randomized, double-blind, placebo-controlled, phase 3 study in adults with gMG. Subjects were randomized and stratified according to three factors: Japanese versus non-Japanese, AChR-Ab seropositive versus AChR-Ab seronegative, and concomitant gMG treatment as nonsteroidal immunosuppressive drugs (NSIDs) versus no NSID.

The total study duration was up to 28 weeks and included a 2-week screening period and an initial 8-week TC, which was followed by an intertreatment cycle (ITC) of variable length depending on the subject's clinical response to efgartigimod. Each 8-week TC comprised a 3-week treatment period and a 5-week follow-up period. At the end of each TC, subjects received only concomitant gMG treatment, and the frequency of visits to the clinic was reduced from

weekly to every 2 weeks. For analysis purposes, the TC and ITC were grouped into cycles. Subsequent TCs were initiated based on the subject's clinical response as measured by the MG-ADL scale. The ITC period consisted of visits every 2 weeks, starting 14 days (±2 days) from the last visit of the previous cycle. At each ITC visit, retreatment criteria were evaluated to determine if the subject entered in the next cycle for retreatment. The study design is shown in the Figure 1.

Figure 1. Study 1704 Design



Source: Protocol Study 1704
Abbreviations: ITC, intertreatment cycle; SoC, standard of care; TC, treatment cycle; V, visit

Criteria for Starting a New Treatment Cycle (Retreatment)

Each subject started a new TC with efgartigimod or placebo when all of the following criteria were met:

- The subject had completed the previous TC (i.e., an 8-week time period after first dosing date) AND
- The subject had a total MG-ADL score of ≥5 points with more than 50% of the total score due to nonocular symptoms AND
- The TC started on Day 127, at the latest, and was completed within the timeframe of the trial (26 weeks) AND
- If the subject was an MG-ADL responder at the previous TC, he/she had lost the response.

Loss of response was defined as a subject who no longer showed a decrease of at least 2 points on the total MG-ADL score compared to the corresponding TC baseline.

However, subjects could not receive retreatment with efgartigimod or placebo if, at the time of retreatment, subjects had clinical evidence of bacterial, viral, or fungal disease, or any other significant disease that could confound the results of the trial or put subjects at undue risk.

Subjects in need of an additional treatment but who were not eligible to receive retreatment remained in the trial to receive appropriate alternative MG treatment. Retreatment with efgartigimod was allowed when conditions for retreatment were met, providing that at least 4 weeks had passed after other MG treatment.

Primary Efficacy Endpoint

The primary efficacy endpoint for Study 1704 was the percentage of AChR-Ab seropositive subjects who, after the first treatment cycle, had a decrease of at least 2 points on the total MG-ADL compared to baseline for at least 4 consecutive weeks, with the first of these decreases occurring, at the latest, 1 week after the last infusion of efgartigimod (i.e., responders).

The MG-ADL is a categorical patient-reported outcome scale (Figure 2) that assesses the impact on daily function of 8 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 0 to 24).

Reviewer's comment*: The Division had previously agreed with the acceptability of the MG-ADL scale as a primary endpoint. The Division had recommended change from baseline on the MG-ADL for the primary analysis but had no objections to the Applicant's proposal to use a responder definition. There is also regulatory precedent for the use of the MG-ADL as a clinical endpoint for gMG, as it was also used in the clinical studies that led to the approval of eculizumab for gMG.*

Figure 2. Myasthenia Gravis Activities of Daily Living (MG-ADL) Scale

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 et al. 2011)

Key Secondary Efficacy Endpoints for Study 1704

The five key secondary endpoints are outlined in Section 6.2.1.3. The first key secondary endpoint utilized a responder definition for the QMG score (Figure 3).

The QMG, shown in Figure 3, 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 quantitatively assessed and graded from 0 to 3, with 3 being the most severe, providing a total QMG score ranging from 0 to 39. The use of a 3-point threshold for a clinically meaningful change of the QMG score is supported by the literature (Katzberg et al. 2014).

***Reviewer's comment**: The QMG score is adequate as a secondary endpoint and was previously used to support the approval of eculizumab.*

Figure 3. 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: (Barohn 2000)

6.2.1.2. Eligibility Criteria, Study 1704

***Reviewer's comment**: The criteria listed below from the submitted protocol appear adequate to enroll subjects with gMG representative of the U.S. population.*

Key Inclusion Criteria

To participate in this study, candidates were required to meet the following eligibility criteria at screening:

- Male or female subjects aged ≥18 years.
- Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) class II, III, IVa, and IVb. The MGFA classification scale is shown in Figure 4.

Figure 4. Myasthenia Gravis Foundation of America (MGFA) Classification Scale

MGFA Clinical Classification

Class I:	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
Class II:	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class III:	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class IV:	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class V:	Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Source: Myasthenia Gravis Foundation of America Task Force

- The confirmation of the diagnosis had to be documented and supported by at least one of the following three tests:

- History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation, or
- History of positive edrophonium chloride test, or
- Subject had demonstrated improvement in MG signs on oral acetylcholinesterase (AChE) inhibitors, assessed by the treating physician.
    - A total MG-ADL score of ≥5 points at screening and baseline (SEB) with more than 50% of the total score due to nonocular symptoms.
    - Subjects were required to be on a stable dose of their MG standard-of-care treatments prior to screening. The standard-of-care was limited to AChE inhibitors, steroids, and NSIDs. For subjects receiving NSIDs, steroids, and/or AChE inhibitors as concomitant medications, the following stability dose conditions applied:
- NSIDs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months prior to screening and no dose changes in the last 3 months before screening.
- Steroids: treatment initiated at least 3 months prior to screening and no dose changes in the last month before screening.
- AChE inhibitors: stable dose with no dose escalation in the past 2 weeks before screening.

Key Exclusion Criteria

Subjects meeting any of the following criteria were not eligible for the study:

- Pregnant and lactating women
- MGFA Class I and V subjects
- Subjects with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, fluoroquinolones, beta-blockers, etc.)
- Subjects with known seropositivity or who test positive for an active viral infection at screening
- Subjects with any known severe bacterial, viral, or fungal infection or any major episode of infection
- Subjects with known autoimmune disease other than MG
- Thymectomy when performed less than 3 months prior to screening

6.2.1.3. Statistical Analysis Plan, Study 1704

Efficacy analyses were based on the modified intent-to-treat analysis set, defined as all randomized subjects with a value for the MG-ADL total score at baseline and at least one postbaseline timepoint. The AChR-Ab seropositive subset population was defined based on the stratification factor as randomized.

The primary endpoint (MG-ADL responder) was defined as the percentage of subjects who, after the first cycle, had a decrease of ≥2 points on the total MG-ADL score (compared to the baseline of the first cycle (C1B)) for at least 4 consecutive weeks (i.e., the next 4 consecutive visits after onset) with the first of these decreases occurring, at the latest, 1 week after the last infusion of the investigational medicinal product (IMP) in AChR-Ab seropositive subjects.

The secondary endpoints were as follows:

- Percentage of subjects who, after the first TC, had a decrease of at least 3 points on the total QMG score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring, at the latest, 1 week after the last infusion in AChR-Ab seropositive subjects.
- Percentage of MG-ADL responders in the overall population (AChR-Ab seropositive and AChR-Ab seronegative subjects).
- Percentage of time that subjects had a "clinically meaningful improvement" (CMI) in MG-ADL total score compared to baseline at study entry (SEB, which coincides with C1B) during the study (up to and including day 126) in AChR-Ab seropositive subjects. CMI is defined as a decrease of at least 2 points on the total MG-ADL score as compared to baseline.
- Time from Week 4 to qualification for retreatment, as assessed by monitoring the MG-ADL total score (compared to C1B) in the AChR-Ab seropositive subjects.
- Percentage of subjects who, after the TC, had a decrease of at least 2 points on the MG-ADL total score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring, at the latest, after 1 or a maximum of 2 infusions of IMP (early MG-ADL responders) in the AChR-Ab seropositive subjects. In practice, visit Week 2 was the last visit the onset of response could start to be considered an early responder, even in the case of a missed infusion.

The primary endpoint and secondary endpoints were tested in a hierarchical order as listed above to control the type I error.

The primary endpoint of MG-ADL responder was analyzed with an exact test (using logistic regression) at the 2-sided 5% significance level in the AChR-Ab seropositive subjects, stratified for the stratification factors (i.e., Japanese/non-Japanese subjects) and standard-of-care, and by using the baseline MG-ADL total score as a covariate.

A similar logistic regression model was applied to response parameters related to the MG-ADL and QMG scales as that for the primary efficacy endpoint. For analyses related to the overall population, the model included AChR-Ab serostatus as an additional stratification factor.

The percentage of time that subjects had a CMI was analyzed using an analysis of covariance model with treatment and baseline total score as a covariate; the model was stratified for the stratification variables (i.e., Japanese/non-Japanese subjects, standard-of-care).

The time to qualification for retreatment as monitored by MG-ADL total score was analyzed using the log-rank test stratified for the stratification variables.

Handling of Intercurrent Events and Missing Data in the Primary Analysis

In case of initiation of a new MG therapy or change in standard-of-care therapy for any reason, assessments after receipt of a new MG therapy or after a change in standard-of-care were considered as not having achieved the required reduction criterion for responder analyses, or as missing assessments for analysis on actual values and changes from baseline.

Subjects who drop-out or were lost-to-follow-up were treated as nonresponse if they did not achieve an MG-ADL response before.

For intermittent missing data at only 1 of 4 post-onset (O) consecutive analysis windows, if the missing data followed one of four score patterns (OmXXX, OXmXX, OXXmX or OXXXmX), then the subject was considered as having achieved an MG-ADL response, providing that the missing data 'm' was not due to MG disease worsening or an adverse event (AE). If no such pattern was present, the subject was considered as not having achieved an MG-ADL response.

For intermittent missing data following onset of response at ≥2 of 4 consecutive post-onset analysis windows, the subject was considered as not having achieved a sustained response regardless of the reason for missing data.

Sensitivity Analyses

Sensitivity analyses were performed for the primary endpoint by imputing missing values for visits Week 1 to Week 8 as not having achieved a drop of 2 points in MG-ADL total score.

The primary endpoint was also analyzed using a Cochran-Mantel-Haenszel statistic stratified for the stratification factors.

6.2.1.4. Results of Analyses, Study 1704

Demographics for the pivotal placebo-controlled Study 1704 are described in the following tables, based on the submitted data (Table 6, Table 7, Table 8, and Table 9). Study 1704 study enrolled 167 subjects. One hundred eighteen (71%) were female. This sex imbalance is consistent with the natural history of the disease, as described in Section 2.1. At screening, age and race were adequately balanced between the placebo and efgartigimod groups.

Reviewer's comment*: Overall, there appears to be an acceptable balance of demographic characteristics between the control and treatment groups that adequately represents the demographics of the intended patient population.*

Table 6. Baseline Demographic and Clinical Characteristics, Study 1704

Characteristic	Efgartigimod (N=84)	Placebo (N=83)	All (N=167)
Sex, n (%)			
Female	63 (75.0)	55 (66.3)	118(70.6)
Male	21 (25.0)	28 (33.7)	49 (29.3)
Age, years			
Mean (SD)	45.9 (14.4)	48.2 (15.0)	47 (15.0)
Median (min, max)	45.0 (19.0, 78.0)	46.0 (19.0, 81.0)	45 (19, 81)
Age group, years			
18 - <65	73 (86.9)	69 (83.1)	142 (85.0)
≥65	11 (13.1)	14 (16.9)	25 (15.0)
Ethnicity, n (%)			
Missing	8 (9.5)	7 (8.4)	15 (9.0)
Hispanic or Latino	7 (8.3)	2 (2.4)	9 (5.4)
Not Hispanic or Latino	69 (82.1)	73 (88.0)	142 (85.0)
Not reported	0	1 (1.2)	1 (0.6)
Race, n (%)			
American Indian or Alaska Native	2 (2.4)	0	2 (1.2)
Asian	9 (10.7)	7 (8.4)	16 (9.6)
Black or African American	3 (3.6)	3 (3.6)	6 (3.6)
Multiple	1 (1.2)	0	1 (0.6)
White	69 (82.1)	72 (86.7)	141 (84.4)
Not reported	0	1 (1.2)	1 (0.6)

Characteristic	Efgartigimod (N=84)	Placebo (N=83)	All (N=167)
Region			
Japan	8 (9.5)	7 (8.4)	15 (9.0)
United States	25 (29.8)	15 (18.1)	40 (24.0)
Rest of world	51 (60.7)	61 (73.5)	112 (67.1)
BMI (kg/m^2)			
Mean (SD)	29 (8)	28 (6)	28 (7)
Median (min, max)	28 (17, 65)	28 (17, 44)	28 (17, 65)
AChR-Ab status			
Positive	65 (77.4)	64 (77.1)	129 (77.2)
Negative	19 (22.6)	19 (22.9)	38 (22.8)

Source: adsl.xpt; Software: Python and Clinical Safety Reviewer
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; BMI, body mass index; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 7. Patient Screening and Randomization, Study 1704

Screening Disposition	Study ARGX-113-1704
Patients screened	216
Not randomized	49
Screening failures	49
Patients randomized	167

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

Table 8. Subject Disposition, Study 1704

Disposition Outcome	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Discontinued study drug	5 (6.0)	10 (12.0)
Adverse event	3 (3.6)	2 (2.4)
Rescue therapy	1 (1.2)	2 (2.4)
Prohibited medications	1 (1.2)	0
Sponsor decision	0	1 (1.2)
Withdrawal by subject	0	2 (2.4)
Protocol deviation	0	3 (3.6)

Source: adds.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in specified population or group

Table 9. Other Baseline Characteristics Including Baseline Concomitant Medications

Baseline Characteristics	Efgartigimod (N=84)	Placebo (N=83)
Disease duration (time since diagnosis in years)		
Mean in years (SD)	10.1	8.83
Median	8.17	6.86
Min, max	0.9, 51.8	0.2, 36.1
Prior thymectomy, n (%)		
Yes	59 (70.2)	36 (43.4)
Baseline total MG-ADL score		
Mean (SD)	9.2 (2.6)	8.8 (2.3)
Median	9.0	9.0
Min, max	5, 17	5, 16
Baseline QMG score		
Mean (SD)	16.2 (5.0)	15.5 (4.6)
Median	17.0	16.0
Min, max	4, 28	6, 27

Baseline Characteristics	Efgartigimod (N=84)	Placebo (N=83)
Standard of care, n (%)		
Any NSIDs	51 (60.7)	51 (61.4)
Any AChE inhibitor	71 (84.5)	67 (80.7)
Any steroid	60 (71.4)	67 (80.7)
NSIDs, n (%)		
Azathioprine	24 (28.6)	26 (31.3)
Cyclosporine	13 (15.5)	11 (13.3)
Cyclophosphamide	2 (2.4)	2 (2.4)
Methotrexate	0	2 (2.4)
Mycophenolate mofetil	11 (13.1)	7 (8.4)
Tacrolimus	2 (2.4)	3 (3.6)

Source: CSR Study 1704 Table 14.1.2.2.3 Baseline Disease Characteristics; Table 17: Concomitant Therapy
Abbreviations: AChE, acetylcholinesterase; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; N, number of subjects in treatment arm; n, number of subjects with given characteristic; NSID, nonsteroidal immunosuppressive drug; QMG, Quantitative Myasthenia Gravis; SD, standard deviation

Efficacy Results – Primary Endpoint

A statistically significantly higher percentage of MG-ADL responders was observed in the efgartigimod group (67.7%) compared to the placebo group (29.7%) during cycle 1 in the AChR-Ab seropositive population (odds ratio [OR] =4.95, p<0.0001; Table 10). Results from the prespecified sensitivity analyses are consistent with the primary analysis.

Table 10. MG-ADL Responders in the AChR-Ab Seropositive Population During Cycle 1

Analysis Type	Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod vs. Placebo	
			Odds Ratio (95% CI)	P-value
Exact test using logistic regression (primary analysis)				
n (%)	44 (67.7)	19 (29.7)	4.95 (2.21, 11.53)	<0.0001
Exact test using logistic regression based on imputed data (sensitivity analysis)				
n (%)	40 (61.5)	19 (29.7)	3.75 (1.70, 8.52)	0.0006
Cochran-Mantel-Haenszel test (sensitivity analysis)				
n (%)	44 (67.7)	19 (29.7)	5.06 (2.33, 11.00)	<0.0001

Source: CSR Tables 19, 14.2.1.4.1, and 14.2.1.3, confirmed by the reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; N, number of subjects in treatment group; n, number of subjects with given characteristic

***Reviewer's comment**: The primary endpoint result, the number of MG-ADL responders after one cycle of treatment, indicates an improvement in activities of daily living, including motor function, in a greater number of subjects treated with efgartigimod compared to subjects given placebo and supports the efficacy of efgartigimod.*

Efficacy Results – Secondary and Other Relevant Endpoints

A statistically significantly higher percentage of QMG responders in the AChR-Ab seropositive population was observed in the efgartigimod group compared to the placebo group during cycle 1 (p<0.0001; logistic regression testing). The QMG responder criterion was met in 41 (63.1%) seropositive subjects in the efgartigimod group compared to 9 (14.1%) seropositive subjects in the placebo group, and the OR (95% confidence interval [CI]) was 10.84 (4.18; 31.20).

Two subjects were not included in the primary analysis of QMG due to missing baseline QMG values. The reviewer conducted two sensitivity analyses: (1) imputed the baseline value using the average baseline QMG value in the AChR-Ab Seropositive Population; (2) performed the

logistic regression without the baseline value as a covariate. The results were consistent with the primary analysis of QMG (Table 11).

Table 11. QMG Responders in the AChR-Ab Seropositive Population During Cycle 1

Analysis Type	Efgartigimod n/N (%)	Placebo n/N (%)	Efgartigimod vs. Placebo Odds Ratio (95% CI)	Efgartigimod vs. Placebo P-value
Primary analysis				
QMG responder	41/65 (63.1)	9/62 (14.5)	10.842 (4.179, 31.200)	<0.0001
Sensitivity analysis (with imputed baseline value for 2 subjects)				
QMG responder	41/65 (63.1)	9/64 (14.1)	10.842 (4.179, 31.200)	<0.0001
Sensitivity analysis (without baseline value as a covariate)				
QMG responder	41/65 (63.1)	9/64 (14.1)	11.707 (4.527, 33.621)	<0.0001

Source: statistical reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; QMG, Quantitative Myasthenia Gravis; N, number of subjects in treatment group; n, number of subjects with given characteristic

A statistically significantly higher percentage of MG-ADL responders was observed in the efgartigimod group compared to the placebo group during cycle 1 in the overall population (p<0.0001; logistic regression testing). The MG-ADL responder criterion was met in 57 (67.9%) subjects in the efgartigimod group compared to 31 (37.3%) subjects in the placebo group, and the OR (95% CI) was 3.70 (1.85; 7.58) (Table 12). The result for the overall population was driven by the AChR-Ab seropositive population (b) (4) (see Section 15 for further details).

Table 12. MG-ADL Responders in the Overall Population During Cycle 1

Analysis Type	Efgartigimod n/N (%)	Placebo n/N (%)	Efgartigimod vs. Placebo Odds Ratio (95% CI)	Efgartigimod vs. Placebo P-value
MG-ADL responder	57/84 (67.9)	31/83 (37.3)	3.699 (1.854, 7.578)	0.0006

Source: CSR Table 21, confirmed by statistical reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; N, number of subjects in treatment group; n, number of subjects with given characteristic

The mean (SE) percentage of time AChR-Ab seropositive subjects were reported to be showing a CMI was 48.714 (6.163) in the efgartigimod group compared to 26.649 (6.316) in the placebo group (Table 13). The difference between the efgartigimod group and placebo group was statistically significant (p=0.0001; analysis of covariance).

Table 13. MG-ADL Total Score Clinically Meaningful Improvement Percentage of Time in the AChR-Ab Seropositive Population, mITT Analysis Set

Parameter	Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod vs. Placebo Difference	Efgartigimod vs. Placebo P-value
LS mean (SE)	48.714 (6.163)	26.649 (6.316)	22.065 (5.616)	0.0001
(95% CI)	(36.517, 60.912)	(14.148, 39.151)	(10.949, 33.181)	

Source: CSR Table 22, confirmed by statistical reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; mITT, modified intent-to-treat; N, number of subjects in treatment group; SE, standard error

The median time to qualification for retreatment (Table 14) was 8 days in the placebo group and 35 days in the efgartigimod group, and the difference between the groups was not statistically significant (p=0.2604; log-rank test).

Table 14. Time to Qualify for Retreatment in the AChR-Ab Seropositive Population, mITT Analysis Set

Group	Subjects (%)		Time (days) to Qualify for Retreatment Since Week 4 Visit			Efgartigimod vs. Placebo P-value
	With Event	Censored	Q1 (95% CI)	Median (95% CI)	Q3 (95% CI)	
Efgartigimod (N=65)	57 (87.7)	8 (12.3)	18.0 (1.0, 29.0)	35.0 (29.0, 43.0)	71.0 (43.0, 114.0)	0.2604
Placebo (N=64)	57 (89.1)	7 (10.9)	1.0	8.0 (1.0; 30.0)	57.0 (34.0; 127.0)	

Source: CSR Table 23, confirmed by statistical reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in treatment group

The percentage of early MG-ADL responders in the AChR-Ab seropositive population was 56.9% in the efgartigimod group and 25.0% in the placebo group. Formal testing was not conducted as the previous endpoint (time to qualification for retreatment) in the testing order was not statistically significant.

6.3. Key Review Issues Relevant to Evaluation of Benefit

(b) (4)

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(b) (4)

6.3.2. Length of Treatment Cycles and the Time Between Treatment Cycles

Issue

How long should a treatment cycle with efgartigimod last and when should repeat treatment cycles be given?

Background

The Applicant's proposed prescribing information provides the following information about treatment cycles and retreatment with efgartigimod following the completion of a treatment cycle:

(b) (4)

(b) (4)

The design of treatment cycles in Study 1704 (Section 6.2.1.1) shows that there was a 4-week follow-up period after completion of treatment. The intertreatment cycle period consisted of visits every 2 weeks, starting 14 days (±2 days) from the last visit of the previous cycle. In other words, the earliest retreatment could begin approximately 4 weeks after the last dose of the previous treatment cycle.

The criteria for starting a new treatment cycle of efgartigimod in Study 1704 are described in Section 6.2.1.1. These criteria are based on the MG-ADL score. (b) (4) Prescribing physicians and patients would need to decide on both initial treatment and retreatment for myasthenia gravis based on clinical examination and the patients' perception of their clinical status.

Assessment

Table 20 shows the duration of MG-ADL response (at least a 2-point improvement from baseline) in Study 1704. All MG-ADL responders who met the primary efficacy endpoint had 4 weeks of response, as defined for the primary endpoint of the study. Eighty-four percent of MG-ADL responders had an onset of response by Week 2 of the treatment cycle (second dose). By 6 weeks after the first 2-point MG-ADL improvement, 89% of subjects remained MG-ADL responders. By 8 weeks after the first 2-point MG-ADL improvement, 57% of subjects remained MG-ADL responders.

Table 20. MG-ADL Response Onset and Duration in the AChR-Ab Seropositive Population During Cycle 1, Study 1704

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

Source: Study 1704 Clinical Study Report
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living

Table 21 shows the treatment cycle durations for the open-label extension Study 1705. Note that the cycle durations have a general pattern of 4 weeks of treatment and approximately 4 weeks of follow-up before beginning a new treatment cycle.

Table 21. Cycle Duration in Days, Study 1705

	AChR-Ab Seropositive			AChR-Ab Seronegative			Overall Population		
	EFG-EFG (N=48)	PBO-EFG (N=45)	Total EFG (N=93)	EFG-EFG (N=14)	PBO-EFG (N=18)	Total EFG (N=32)	EFG-EFG (N=62)	PBO-EFG (N=63)	Total EFG (N=125)
Cycle 1, n	33	27	60	9	14	23	42	41	83
Mean (SD)	65.3 (27.64)	69.1 (33.41)	67.1 (30.17)	68.8 (30.76)	57.9 (17.75)	62.1 (23.66)	66.1 (27.98)	65.3 (29.28)	65.7 (28.46)
Median (min, max)	57.0 (29, 172)	52.0 (49, 187)	56.0 (29, 187)	57.0 (35, 140)	50.0 (49, 112)	52.0 (35, 140)	57.0 (29, 172)	50.0 (49, 187)	52.0 (29, 187)
Cycle 2, n	13	12	25	3	8	11	16	20	36
Mean (SD)	60.8 (17.21)	70.8 (47.44)	65.6 (34.73)	60.7 (9.87)	63.6 (27.43)	62.8 (23.41)	60.8 (15.81)	68.0 (39.92)	64.8 (31.39)
Median (min, max)	50.0 (49, 106)	54.0 (48, 217)	52.0 (48, 217)	56.0 (54, 72)	50.0 (49, 127)	54.0 (49, 127)	55.0 (49, 106)	51.5 (48, 217)	53.0 (48, 217)
Cycle 3, n	9	8	17	1	6	7	10	14	24
Mean (SD)	49.9 (19.37)	59.4 (11.73)	54.4 (16.48)	51.0	51.3 (4.27)	51.3 (3.90)	50.0 (18.27)	55.9 (9.91)	53.5 (13.97)
Median (Min, max)	51.0 (4, 78)	55.0 (50, 83)	52.0 (4, 83)	NA	50.0 (49, 60)	50.0 (49, 60)	51.0 (4, 78)	50.0 (49, 83)	50.5 (4, 83)
Cycle 4, n	3	1	4	0	1	1	3	2	5
Mean (SD)	52.3 (4.04)	50.0	51.8 (3.50)	--	50.0	50.0	52.3 (4.04)	50.0 (0.00)	51.4 (3.13)
Median (min, max)	50.0 (50, 57)	NA	50.0 (50, 57)	--	NA	NA	50.0 (50, 57)	50.0 (50, 50)	50.0 (50, 57)

Source: CSR Study 1705
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; EFG, efgartigimod; NA, not applicable; PBO, placebo; SD, standard deviation

Based on the above data from Studies 1704 and 1705, most myasthenia gravis subjects who respond to an initial treatment with efgartigimod would be expected to need retreatment approximately 4 weeks after the last efgartigimod infusion.

The minimum time to initiation of another treatment cycle, defined by protocol in Part A of Study 1705, was 50 days. The reader is referred to Section 7.5 for further details on the assessment of the adequacy of the clinical safety database and duration of treatment cycles observed in pooled Studies 1704, 1602, and 1705.

Conclusion

Treatment periods should last 4 weeks (i.e., 4 once weekly infusions), as was conducted in the pivotal efficacy Study 1704 and described in the proposed prescribing information.

Based on the data from Study 1705, it is expected that retreatment would be clinically indicated in most myasthenia gravis patients approximately 4 weeks after completion of a prior treatment period.

Safety data are limited on treatment cycles shorter than 50 days, based on minimum protocol-defined intertreatment periods in Study 1705. There is inadequate safety data to recommend initiation of a treatment cycle sooner than 50 days; however, this should be sufficient to allow most patients to be treated when it is anticipated to be clinically indicated (i.e., approximately 4 weeks after completion of a prior treatment period).

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The pivotal toxicology studies submitted to BLA 761195 consisted of 28-day studies in Sprague-Dawley rat (0, 10, 30, and 100 mg/kg Q2D) and cynomolgus monkey (0, 3, 30, and 100 mg/kg Q2D), a 26-week study in cynomolgus monkey (0, 10, 30, and 100 mg/kg QW), and a complete battery of reproductive and developmental toxicology studies in Sprague-Dawley rat (0, 30, and 100 mg/kg QD) and New Zealand White rabbit (0, 30, and 100 mg/kg QD). All studies used IV administration. In the 28-day studies, microscopic findings were observed at the injection site reactions (e.g., hemorrhage and necrosis in rat and monkey) and in liver (Kupffer cell hypertrophy/hyperplasia [rat] and hepatocellular degeneration [monkey]). However, in the 26-week monkey study, no treatment-related toxicity was observed, indicating less toxicity with the longer dosing interval used. The NOAEL for the 26-week study was determined to be the high dose of 100 mg/kg/week, associated with plasma $AUC_{0-\infty}$ of 20687µg*h/mL for males and 18091µg*h/mL for females.

No adverse reproductive or developmental effects were observed in rat or rabbit.

As is typical for biologic products, no genotoxicity or carcinogenicity studies were conducted with efgartigimod.

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

The proposed mechanism of action of efgartigimod is to bind to the neonatal Fc receptor. Hypoalbuminemia was of concern because the Fc receptor is involved in the maintenance of serum albumin levels. Hypoalbuminemia is explored in Section 7.7.2.

Cholesterol levels were of special interest because it has been reported that treatment with IMVT-1401, a human monoclonal antibody developed for thyroid eye disease that targets the neonatal Fc receptor, elevated low-density lipoprotein (LDL) levels by 60% after 12 weeks of therapy (Mast 2021). Cholesterol is explored in Section 7.7.2.

Infections were of special interest because efgartigimod results in a reduction of circulating IgG, which potentially increases the risk for infection. Infections are explored in Section 7.7.1.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. Efgartigimod is a new molecular entity. It is not approved in other regions of the world.

7.4. FDA Approach to the Safety Review

Clinical trial 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 issues identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in Studies 1704, 1602, and 1705 were reviewed and found to be acceptable. Treatment-emergent AEs (TEAEs) in Studies 1704 and 1705 were protocol-defined as any AE temporally associated with the use of the IMP, whether considered related to the IMP or not. TEAEs in Study 1602 were protocol-defined as an AE that first occurred or worsened in severity after the first administration of the IMP. All AEs in the reviewed trials were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0 for Studies 1704 and 1705; version 4.03 for Study 1602), which was reviewed and found to be acceptable.

Data from completed placebo-controlled Studies 1602 and 1704 and from ongoing open-label, long-term extension Study 1705 formed the basis of the clinical safety evaluation. Study 1704 is the primary source of evidence of effectiveness, and results for this study are presented individually in this review. Data that are presented for this study include findings that occurred in subjects who received up to three treatment cycles, which is the maximum number a subject could receive by protocol. Safety data from Study 1704 will provide the primary description of safety, with Studies 1602 and 1705 providing supportive data.

Section 7.6.1 presents the safety data for the double-blind placebo controlled pivotal study 1704 alone. Section 7.6.2 presents pooled data for studies 1704 and the phase 2 placebo-controlled study 1602. Section 7.6.3 presents pooled data for studies 1704, 1602, and the ongoing long-term extension study 1705. Section 7.7 presents key safety issues. Additional supportive information and assessments are found in Section 17.

A summary of the study designs can be found in Sections 6.2, 16, and 17.1. Of note, in Studies 1602 and 1704, changes to concomitant generalized myasthenia gravis therapies were not permitted. Subjects were discontinued from the study if they required rescue therapy based on clinical deterioration. In Study 1705, rescue therapy was permitted but was limited to plasma exchange, intravenous immunoglobulin, immunoadsorption, a new type of corticosteroid, or an increased dose of the current corticosteroid as stand-alone or in combination.

Refer to Section 17.1 for a detailed description of the study design and eligibility criteria for Study 1705.

The following table (Table 22) lists safety pools used in this review.

Table 22. Myasthenia Gravis Safety Pools by Trial

Name of Pool	Description	Efgartigimod 10 mg/kg	Placebo
PB1	Placebo-controlled phase 2 Study 1602 that had only one treatment cycle and phase 3 Study 1704 using first treatment cycle only to allow for comparison of similar exposure periods	96	95
PB2	All efgartigimod-treated in subjects in Studies 1602, 1704, and 1705; in subjects treated for up to 11 treatment cycles	162	Not applicable

Source: Safety Reviewer
Abbreviations: PB1, Pooling Block 1; PB2, Pooling Block 2

Overall, the reviewer found the Applicant's approach for pooling of data listed above to be acceptable.

Adverse events related to death, serious adverse events (SAEs), and cases potentially meeting Hy's law criteria in the three additional studies in the clinical program were reviewed. Studies 1501 and 1702 were phase 1 studies performed in healthy subjects. Study 1603 was a phase 2 study performed for the indication of treatment of primary immune thrombocytopenia. Of note, the Applicant included Study 1603 in a third pooling block with Studies 1602, 1704, and 1705. The reviewer did not find this pooling strategy to be as informative because of differences in risk for adverse events based on differences in disease states (e.g., subjects with immune thrombocytopenia would be at a higher risk for bleeding compared to those with myasthenia gravis).

The reviewer evaluated the Applicant's translation of adverse events from verbatim terms to preferred terms for Studies 1602, 1704, and 1705, and the translations appeared adequate, except that the reviewer recoded one preferred term in Study 1704 from contusion to fall in order to better capture the event of fall. The reported term was "bruising on abdomen and anterior leg – fell at work after losing balance" (Subject (b) (6)).

In a response dated August 24, 2021, to an information request dated August 20, 2021, the Applicant noted that the TEAEs of palpitations and nausea, reported by Subject (b) (6), were not included in the 90-Day Safety Update clinical database due to delayed entry in the clinical database. They stated that the reason for the delayed data entry was unknown.

7.5. Adequacy of Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of efgartigimod for the proposed indication, patient population, dosage regimen, and duration. Because generalized myasthenia gravis is a rare disease, the Division agreed with the Applicant that the exposure of the safety database is adequate in terms of size and dosing.[1] As outlined by the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, a lower number of subjects exposed to the drug than the number proposed in the E1 guideline may be acceptable if the intended treatment population is small. The database includes 162 subjects with myasthenia gravis who were dosed intravenously at least once with efgartigimod 10 mg/kg. Across the clinical program, 246 subjects received at least one dose of efgartigimod for treatment

[1] Noted in an email communication dated October 14, 2020.

of myasthenia gravis. Prior to the 90-Day Safety Update, the Applicant noted 83 subjects had follow-up of at least 12 months and 43 subjects had at least 7 cycles with a follow-up of at least 12 months, in agreement with the Division. At the time of the 90-Day Safety Update, 57 subjects who had started at least 7 cycles had at least 6 months of follow-up and 48 of the 57 subjects had at least 12 months of follow-up. The reviewer notes that safety data are limited on treatment cycles shorter than 50 days based on minimum protocol-defined intertreatment periods in Study 1705 and recommends informing prescribers that the safety of initiating a treatment cycle sooner than 50 days from the start of the previous cycle has not been established.

Refer to the Appendix 17.2 for a table of subjects enrolled across phase 1, 2, and 3 studies by population type.

The following table (Table 23) indicates the number of subjects who started at least one or had at least seven cycles of efgartigimod and who had at least 12 months of follow-up in pooled Studies 1602, 1704, and 1705 prior to the 90-Day Safety Update.[2]

Study 1704 was the only trial that contributed to safety that had subjects who had at least 6 months of exposure compared to placebo. In this trial, seven subjects who started at least one cycle of placebo had 6 months of follow-up.

Table 23. Duration of Follow-Up in Subjects Who Started at Least 1 Cycle or at Least 7 Cycles of Efgartigimod, Pooled Studies 1602, 1704, and 1705.

Number of Cycles	≥6 Months Follow-Up	≥12 Months Follow-Up	≥18 Months Follow-Up
At least 1	139	76	11
At least 7	43	38	8

Source: This table was created by the reviewer using ISS PB2 ADAPER dataset.
For subjects who started at least X cycles, Actual Pooled Treatment Group 1 = total efgartigimod, Pooled Subject Group 1 = greater than or equal to X cycles, Grouped by USUBJID and minimum Period Start Datetime and maximum Period End Datetime; Formula: [(Period Max – Period Min)/(24*3600)] +1 where 6 months ≥182.5 days, 12 months ≥365 days, and 18 months ≥547.5 days

Efgartigimod-treated subjects were exposed to an average of 2 cycles. The mean duration of the first treatment cycle was 94 days (median of 72 days).[3]

The minimum time for a treatment cycle in Study 1704 was 68 days, which was protocol-defined based on a combined treatment period, follow-up period, and minimum intertreatment cycle period. The minimum time for a treatment cycle in Part A of Study 1705 was 50 days, and was protocol-defined based on a combined treatment period and minimum intertreatment cycle period.

The reviewer notes that safety data are limited on treatment cycles shorter than 50 days based on the minimum protocol-defined intertreatment cycle period in Part A of Study 1705. The Applicant has proposed in labeling that efgartigimod be administered in treatment cycles of once weekly infusions for 4 weeks and that patients should be retreated according to clinical evaluation. The reviewer recommends informing prescribers that the safety of initiating

[2] The Applicant noted 83 subjects who at received at least one cycle of efgartigimod and had 12 months of follow up (Table 6 on page 31 of the Summary of Clinical Safety 1) and 43 subjects who received at least seven cycles of efgartigimod and had 12 months of follow up. The Applicant's numbers differ from the reviewer's numbers because of differences in rounding methods (the Applicant defined 12 months as >350 days whereas reviewer defined 12 months as ≥365 days).
[3] Noted by the Applicant in the clinical study report for Study 1704, Appendix 14, Tables 14.2.1.6.2 and 14.1.1.4.3.

subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.

To estimate actual duration of a treatment cycle observed in clinical trials, the Applicant used two methods of calculation. In the first method (Method 1), the duration of Cycle X was equal to the number of days between the first infusion of Treatment Cycle X and the first infusion of Treatment Cycle X +1, and was based on subjects who had received at least X cycles. In the second method (Method 2), the duration of Cycle X was equal to the time between the first infusion of the first treatment cycle and the end of Treatment Cycle X (defined as the Cumulative Treatment Cycle) divided by X, and was based on subjects who had received a maximum of X cycles.

To estimate actual duration of a treatment cycle, the reviewer excluded subjects whose treatment cycles were potentially cut short by the data cutoff, which resulted in slight differences in the duration of treatment cycles in the reviewer's calculations compared to the Applicant's.[4]

The following table (Table 24) shows the duration of the seventh treatment cycles using the two methods for calculation for pooled Studies 1602, 1704, and 1705.

Table 24. Mean Duration of the Seventh Treatment Cycle Using Methods 1 and 2, Pooled Studies 1704, 1602, and 1705

Method 1 (days)[1]			Method 2 (days)[2]			
Mean Duration Cycle 7 (SD)	Median	Min, Max	Mean Duration Cycle 7	Cumulative Duration for Cycles 1 to 7 Mean (SD)	Median	Min, Max
58 (14)	51	49, 106	58	417 (60)	408	354, 597

Source: Safety Reviewer
[1] Calculated using ISS PB2 Oct cutoff date ADAPER dataset, Pooled Subject Group 1=7, 8, 9, 10, and 11 cycles; Period C = Cycle 7; Period End Date Imput. Flag = Inverse of Yes; Tabulate on Period Duration. The period duration is defined as the number of days from the first infusion of a cycle to the first infusion of the next cycle. (This analysis excludes subjects whose cycles were cut short because of the data cutoff).
[2] Calculated based on the formula of the median Cumulative Cycle Duration (in days) for Cycle X/X. This table was created by the reviewer using ISS PB2 ADAPER dataset, where Cumulative Cycle Duration in Days = [(Period End Datetime - Phase Start Datetime)/(24 x 60 x 60)] +1; for Cycle X, Pooled Subject Group 1 = X cycles and Period C = X cycles.
Abbreviations: SD, Standard Deviation.

90-Day Safety Update for Exposure

At the time of the 90-Day Safety Update, no new subjects had been enrolled in Study 1705. Six subjects had received their first efgartigimod dose in Study 1705; however, all six had received efgartigimod in the antecedent trial. Fifty-seven subjects had received at least 7 cycles and 8 subjects had received at least 10 cycles.

The number of subjects who started at least 7 cycles and had 6-months of follow-up had increased from 27% (43/162) in the original submission to 35% (57/162) in the 90-Day Safety Update.

The frequency of subjects who started at least 7 cycles of efgartigimod and had at least 12-months of follow-up was similar to the original submission (30% [48/162 subjects] versus 23% [38/162 subjects], respectively).

[4] The Applicant calculated a median duration of 50 days (mean of 44 days) for Cycle 7 (see page 2 of Table 14.1.1.2.3, with link to the table located on page 30 of the ISS Summary of Clinical Safety 1).

After the 90-Day Safety Update, the median duration of the seventh treatment cycle using calculation Method 1 increased from 51 to 54 days in pooled Studies 1704, 1602, and 1705.

The average cycle duration using calculation Method 2 remained the same after the 90-Day Safety Update in Pooled Studies 1704, 1602, and 1705 (58 days).

The maximum number of treatment cycles a subject could be exposed to increased from 11 to 13.

Refer to Section 17.3 for updated tables on exposure and cycle duration after the 90-Day Safety Update.

Relevant Characteristics of the Safety Population

In Study 1704, the efgartigimod arm had a higher percentage of subjects who were female compared to the placebo arm (75% versus 66%, respectively). A higher percentage of efgartigimod-treated subjects were from the United States compared to placebo (30% versus 18%, respectively). The mean age of a subject in Study 1704 was 47 years. Eighty-five percent of subjects were 65 years and over, and 4% were 75 years and older. Refer to Table 6 for baseline demographics for the safety population in Study 1704.

The reviewer notes that demographic characteristics in Study 1704 were similar to demographics observed in two published cohort studies of over 500 subjects with generalized myasthenia gravis from the U.S. population (Grob et al. 2008; Harris et al. 2020)(Grob et al. 2008; Harris et al. 2020). The percentage of females in Study 1704 was similar to the percentage of females with generalized myasthenia gravis observed by Harris et al. and Grob et al. (71% versus 61% and 62%, respectively). The study by Harris et al. also included data on mean age and race of subjects within the cohort. A similar mean age and percentage of white subjects was observed in Study 1704 compared to the cohort study by Harris et al. (mean age of 47 years versus 57 years, respectively; percentage of white subjects was 84% versus 74%, respectively).

Similar to Study 1704, pooled Studies 1602 and 1704 had a higher percentage of subjects from the United States in the efgartigimod 10 mg/kg arm compared to placebo (28% versus 18%, respectively).

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

If efficacy is demonstrated and the benefits of efgartigimod outweigh the risks, then the reviewer recommends that approval include appropriate labeling language to address the frequency of dosing and adverse reactions of concern. The reviewer notes that the assessment of AEs with efgartigimod treatment was limited by the small number of subjects in Studies 1704, 1602, and 1705 (n=162). A conclusion regarding the carcinogenicity of efgartigimod could not be drawn because of the small number of subjects and short mean duration of exposure to efgartigimod (369 days for subjects receiving at least one cycle of efgartigimod) in Studies 1704, 1602, and 1705.

A total of five deaths occurred in the clinical safety database after the 90-Day Safety Update, all occurring in the long-term extension Study 1705. Two deaths occurred in the setting of infection, and a role for efgartigimod could not be ruled out as infections were among the most frequently

reported AEs in Study 1704 and pooled Studies 1704 and 1602. Both cases had potential contributory factors related to infection. In the three remaining cases of death, the reviewer did not identify a role for efgartigimod. The overall incidence of death across the clinical program for the myasthenia gravis indication in efgartigimod-treated subjects was 2% (5/246).

The overall incidence of SAEs in the efgartigimod arm was comparable to placebo in Study 1704 and pooled Studies 1602 and 1704. The most frequently reported SAEs by preferred term in the efgartigimod arms occurred with similar frequency in placebo arms in Study 1704 and pooled Studies 1602 and 1704 (difference no greater than 1%). In pooled Studies 1602, 1704, and 1705, infection, myasthenia gravis, and malignancy were the most frequently reported SAEs.

The reviewer could not rule out a role for efgartigimod in SAEs related to infection given that infections were among the most frequently reported AE in clinical trials. Other potential contributory factors existed in the cases of SAEs related to infection. Additionally, the reviewer could not rule out a role for efgartigimod in one SAE related to depression, given a lack of known risk factors. Refer to Section 17.3.2 for a review of narratives of SAEs in Studies 1602, 1704, and 1705.

AEs leading to trial or treatment discontinuation were reported with low frequency in efgartigimod-treated subjects in Study 1704 (4% or less). In pooled Studies 1704, 1602, and 1705, 3% of subjects reported AEs leading to trial discontinuation and 7% reported AEs leading to treatment discontinuation. Myasthenia gravis, coronavirus disease 2019 (COVID-19) pneumonia, and malignancy were the most frequently reported AEs leading to treatment discontinuation in pooled Studies 1602, 1704, and 1705. No AEs led to trial or treatment discontinuation in Study 1602. Refer to Section 17.4 for a list of reasons for trial and treatment discontinuation by protocol in Studies 1704, 1602, and 1705.

The most frequently reported TEAEs in Study 1704 were upper respiratory tract infection, urinary tract infection (UTI), and myalgia. Similar findings were observed in pooled Studies 1602 and 1704. In Study 1704, upper respiratory tract infection occurred in 11% of efgartigimod 10 mg/kg-treated subjects versus 5% for placebo. UTI occurred in 10% of efgartigimod 10 mg/kg-treated subjects versus 5% for placebo. Myalgia occurred in 6% of efgartigimod 10 mg/kg-treated subjects versus 1% for placebo. In pooled Studies 1602, 1704, and 1705, headache, nasopharyngitis, and diarrhea were among the most frequently reported TEAEs and occurred with similar frequency as in Study 1704.

In Study 1704 and pooled Studies 1602 and 1704, the most frequent laboratory abnormalities included decreased leukocyte counts and decreased lymphocyte counts. In pooled Studies 1704, 1602, and 1705, the most frequent laboratory abnormalities were decreased lymphocytes and increased triglycerides.

No subjects met Hy’s law case criteria in any trials in the clinical program.

7.6.1. Safety Findings and Concerns, Study 1704

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Study 1704

The following table (Table 25) provides a summary of TEAEs in Study 1704. There were no deaths. The overall frequency of a subject experiencing TEAEs, SAEs, or AEs leading to study or trial discontinuation in Study 1704 was comparable between the efgartigimod and placebo

arms. Three SAEs of depression, rectal adenocarcinoma, and thrombocytosis occurred in one efgartigimod-treated subject each.

Table 25. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Study 1704

Event	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Any treatment-emergent AE[1]	65 (77)	70 (84)
Moderate or severe AEs (Grade 3-5)[2]	9 (11)	8 (10)
SAEs	4 (5)	7 (8)
SAEs with fatal outcome	0	0
AEs leading to trial discontinuation	1 (1)	0
AEs leading to discontinuation of study drug	3 (4)	3 (4)

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

7.6.1.2. Deaths, Study 1704

There were no deaths in Study 1704.

7.6.1.3. Serious Adverse Events, Study 1704

Four SAEs occurred in efgartigimod-treated subjects in Study 1704 (depression, rectal adenocarcinoma, thrombocytosis, and myasthenia gravis). Table 26 lists SAEs in Study 1704 with a higher frequency in the efgartigimod arm compared to placebo.

Table 26. Serious Adverse Events, Safety Population, Study 1704

Serious Adverse Event[1]	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Depression	1 (1)	0
Rectal adenocarcinoma	1 (1)	0
Thrombocytosis	1 (1)	0

Source: Clinical Safety Reviewer
[1] Coded as MedDRA preferred term
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Study 1704

In Study 1704, one subject (1%) in the efgartigimod arm reported an adverse event (rectal adenocarcinoma) that led to study withdrawal, while none did in the placebo arm. The Subject ([redacted](b) (6)) was diagnosed 97 days after beginning efgartigimod treatment. Because the subject had risk factors for the AE (positive tobacco history and age >50 years), a role for efgartigimod could not be established.

Three efgartigimod-treated subjects experienced AEs that led to treatment discontinuation. As mentioned above, one of the three subjects had an adverse event of rectal adenocarcinoma that led to trial withdrawal (Subject [redacted](b) (6)). Another subject with AEs of myasthenia gravis, balance disorder, rash, restless leg syndrome, and facial paresis (Subject

[redacted] (b) (6)) and a third with an AE of thrombocytosis (Subject [redacted] (b) (6)) are discussed in Section 17.3.2.

Table 27 shows TEAEs leading to treatment discontinuation with a higher frequency in the efgartigimod arm compared to placebo in Study 1704.

Table 27. Adverse Events Leading to Treatment Discontinuation With Higher Frequency in the Efgartigimod Arm Compared to Placebo, Safety Population, Study 1704

Adverse Event[1]	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Balance disorder	1 (1)	0
Facial paresis	1 (1)	0
Rash	1 (1)	0
Rectal adenocarcinoma	1 (1)	0
Restless legs syndrome	1 (1)	0
Thrombocytosis	1 (1)	0

Source: Clinical Safety Reviewer
[1] Coded as MedDRA preferred terms
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.1.5. Treatment-Emergent Adverse Events, Study 1704

The most frequently reported TEAEs in Study 1704 in efgartigimod-treated subjects were related to infection and included UTI, upper respiratory tract infection, and bronchitis. Infection was a topic of special interest for this review and is discussed further in Section 7.7.

For the creation of the TEAE Table 28, the reviewer used the cut off frequency of at least 5% in the efgartigimod arm and higher frequency than placebo consistent with the cut offs used in labeling for eculizumab, a monoclonal antibody approved for the indication of generalized myasthenia gravis in 2019.

Refer to the Appendix for tables of TEAEs that occurred in Study 1704 at a frequency of at least 5% in the efgartigimod arm and at a higher rate than in the placebo arm, grouped by preferred term, groups of preferred terms, or FDA MedDRA Query Group (Table 78 and Table 79). Also included in the Appendix are preferred terms that were excluded from the FDA MedDRA Query Groups for labeling because they occurred with equal or lower frequency in the efgartigimod arm compared to placebo.

Table 28 includes recommendations for preferred terms or groups of preferred terms for labeling purposes and their frequency in Study 1704.

Table 28. TEAEs That Occurred at a Frequency of at Least 5% in the Efgartigimod 10 mg/kg Arm and at a Higher Rate Than in the Placebo Arm, Study 1704

Preferred Term	Efgartigimod (N=84) %	Placebo (N=83) %
Urinary tract infection	10	5
Myalgia	6	1
Paresthesias[1]	7	5
Respiratory tract infection[2]	33	29
Headache (FDA narrow)[3]	32	29

Source: This table was created by the reviewer using 1704 ADAE dataset, treatment-emergent analysis flag = Y; Group by Unique Subject Identifier, Actual Treatment and Dictionary-Derived Term or FMQ group.
[1] Includes hypoesthesia, hyperesthesia, and hypoesthesia oral.
[2] Includes bronchitis, chronic sinusitis, influenza, nasopharyngitis, pharyngitis, pneumonia, sinusitis, upper respiratory tract infection, viral pharyngitis, and viral tracheitis.
[3] Includes procedural headache, migraine, and headache.
Abbreviations: FMQ, FDA MedDRA query; N, number of subjects in group; TEAE, treatment-emergent adverse event

For labeling purposes, chronic sinusitis, influenza, and nasopharyngitis were excluded from the respiratory tract infection preferred terms listed below the common adverse events table in section 6 of labeling as they did not occur with higher frequency in the efgartigimod arm than in the placebo arm. Refer to Table 79 in the Appendix for groups of preferred terms and FDA MedDRA Queries that occurred at a higher rate in the efgartigimod treatment arm than placebo in Study 1704.

7.6.1.6. Laboratory Findings, Study 1704

Laboratory findings showed a higher frequency of decreased leukocyte count, decreased lymphocyte count, decreased neutrophil count, increased monocyte/leukocyte ratio, and increased c-reactive protein. The reviewer recommends inclusion of decreased leukocyte count, lymphocyte count, and neutrophil count in labeling as infections were observed to be among the most frequently reported AEs in efgartigimod-treated subjects. Refer to the Infections section (Section 7.7.1) for a further review of this topic. The reviewer does not recommend inclusion of other laboratory abnormalities unrelated to leukocytes, lymphocytes, and neutrophils in labeling because the difference between efgartigimod and placebo arms was less than 10%.

The reviewer evaluated mean change from baseline values, outlier shifts by CTCAE Grade severity, outlier shifts to high, low, and abnormal categories, and TEAEs belonging to the system organ classes (SOC) Investigation related to laboratory findings.

Change from Baseline

The reviewer did not identify any clinically significant changes in analyses of mean change from baseline because of small magnitudes of change or because of small sample sizes at visits towards the end of treatment cycles in Study 1704.

Shift Analyses by CTCAE Grade Severity and by High, Low, and Abnormal Values

In Study 1704, the most frequent postbaseline laboratory abnormalities of CTCAE Grade 1 or higher severity were decreased leukocyte count, decreased lymphocyte count, and decreased neutrophil count. An imbalance in these parameters of CTCAE Grade 3 or higher severity was not seen.

The laboratory abnormalities of decreased leukocyte count, decreased lymphocyte count, and decreased neutrophil count had similar maximum lowest values between efgartigimod and placebo arms. The maximum lowest leukocyte count in the efgartigimod arm was 2.6 x 10^3/uL compared to 1.7 x 10^3/uL on placebo (reference range 3.8 to 10.7 x 10^3/uL). The maximum lowest lymphocyte count in the efgartigimod arm was 0.2 x 10^3/uL compared to 0.3 x 10^3/uL on placebo (reference range 0.9 to 4.3 x 10^3/uL). The maximum lowest neutrophil count in the efgartigimod arm was 1.2 x 10^3/uL compared to 0.9 x 10^3/uL, on placebo (reference range 2.0 to 7.2 x 10^3/uL).

Refer to Key Review Issues Relevant to Evaluation of Risk section on Infection (Section 7.7.1) of this review for an analysis of infections related to efgartigimod use and to the Adverse Events in Subjects with Laboratory Abnormalities of CTCAE Grade 3 or Higher Severity section in the Laboratory Findings section of Studies 1704, 1602, and 1705 (Section 7.6.3.6).

Table 29 shows the frequency of subjects with postbaseline laboratory abnormalities of CTCAE Grade 1 or higher severity and at least 5% higher frequency in the efgartigimod arm compared to placebo.

Table 29. Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade 1 Severity or Higher and With Frequency of at Least 5% Higher in the Efgartigimod Arm Compared to Placebo, Safety Population, Study 1704[1]

	Study 1704	
Laboratory Analysis	Efgartigimod n/N (%)	Placebo n/N (%)
Decreased leukocytes	10/81 (12)	4/80 (5)
Decreased lymphocyte	20/72 (28)	14/72 (19)
Decreased neutrophils	11/84 (13)	5/80 (6)
Increased activated partial thromboplastin time	7/83 (8)	2/82 (2)

Source: Clinical safety reviewer
[1] CTCAE grading scale used for toxicity grades where Grade 1 or higher severity for leukocytes is <3.8 x 10^3/uL, lymphocytes is <0.8/0.91 x 10^3/uL, neutrophils is <1.96 x 10^3/uL, activated partial thromboplastin time is >32.5 sec, triglycerides is ≥151 mg/dL.
N is the subjects with normal baseline values
Events are counted only once for subjects with multiple events
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects; n, number of subjects with abnormality

In Study 1704, the only laboratory abnormality of CTCAE Grade 3 or higher severity and with a higher frequency in the efgartigimod arm compared to placebo was increased sodium from Grade 0 at baseline (sodium greater than 155 mEq/L), occurring in two subjects in the efgartigimod arm (2%) compared to no subjects on placebo.

In Study 1704, laboratory abnormalities with a frequency highest in the efgartigimod arm compared to placebo occurred with monocyte/leukocyte shift to high and c-reactive protein shift to high. The maximum monocyte/leukocyte ratio was similar between the efgartigimod and placebo arms (15% versus 16%, respectively).

Table 30 shows laboratory abnormalities with shift to high, low, and abnormal with a frequency of at least 5% higher in the efgartigimod arm compared to placebo in Study 1704.

Table 30. Laboratory Abnormalities With Shift to High, Low, and Abnormal With a Frequency of at Least 5% Higher in the Efgartigimod Arm Compared to Placebo, Safety Population, Study 1704[1]

	Study 1704	
Laboratory Analysis	Efgartigimod n/N (%)	Placebo n/N (%)
Monocytes/leukocytes shift to high	17/78 (22)	7/72 (10)
C reactive protein shift to high	21/79 (27)	15/81 (19)
Hemoglobin shift to low	14/69 (20)	10/76 (13)
Calcium shift to high	11/82 (13)	6/83 (7)
LDL cholesterol shift to low	24/67 (36)	18/59 (31)

Source: Clinical safety reviewer
[1] Shift to high, low, and abnormal category in worst postbaseline value in subjects with a normal baseline value. The reviewer created this table using the 1704 ADLB2 dataset, baseline reference range indicator = normal, analysis reference range indicator = high, low, and abnormal, analysis visit = worst postbaseline visit ANRIND, analysis toxicity grade = missing.
N is the subjects with normal baseline values
Events are counted only once for subjects with multiple events
Abbreviations: LDL, low-density lipoprotein; N, number of subjects; n, number of subjects with abnormality

TEAEs Related to Laboratory Findings

No TEAEs related to laboratory findings had frequency of 5% or greater in the efgartigimod arm in Study 1704. The TEAE of decreased lymphocyte count was reported in one efgartigimod-treated subject compared to none on placebo.

Hepatic-Related Events

The reviewer did not identify a safety signal for hepatic-related events in an analysis of maximum postbaseline liver enzyme values, hepatic-related adverse events, or Hy's law cases in Study 1704.

In Study 1704, the frequency of subjects with maximum postbaseline values meeting cut points above the upper limit of normal for liver enzymes in the efgartigimod 10 mg/kg arm did not exceed placebo by more than 1%. Table 31 shows the maximum postbaseline values for liver enzymes in Study 1704.

Table 31. Maximum Postbaseline Values for Liver Enzymes, Study 1704

Lab Test	Cut Point	Efgartigimod (N=84) n/N (%)	Placebo (N=83) n/N (%)
ALT	>3*ULN	0/84 (0)	1/83 (1)
	>5*ULN	0/84 (0)	0/83 (0)
AST	>3*ULN	0/84 (0)	0/83 (0)
	>5*ULN	0/84 (0)	0/83 (0)
ALP	>1.5*ULN	0/84 (0)	3/83 (4)
BILI	>2*ULN	1/84 (1)	0/83 (0)

Source: This table was created by the reviewer using 1704 ADLB2 dataset
Baseline record flag = inverse of yes; lab test or examination name = ALT, ALP, AST, or BILI; grouped by USUBJID and Numeric Result/Reference Range Upper Limit.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal; N, number of subjects in treatment group; n, number of subjects with given characteristic

No subjects met Hy's law case criteria in Study 1704.

7.6.2. Safety Findings and Concerns, Studies 1602 and 1704

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, Studies 1602 and 1704

Similar to Study 1704 alone, the frequency of a subject reporting at least one SAE in pooled Studies 1602 and 1704 was comparable in the efgartigimod and placebo arms (2% versus 5%, respectively). No AEs were reported to lead to trial or treatment discontinuation. The frequency of subjects experiencing at least one TEAE overall in the efgartigimod arm did not exceed placebo (73% versus 78%, respectively). TEAEs related to infection were the most frequently reported TEAEs in pooled Studies 1704 and 1602.

Table 32 shows an overview of TEAEs in pooled Studies 1602 and 1704.

Table 32. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Study 1602 and 1704

Event	Efgartigimod (N=96) n (%)	Placebo (N=95) n (%)
Any treatment-emergent AE[1]	70 (73)	74 (78)
Moderate or severe AEs (Grade 3-5)[2]	6 (6)	6 (6)
SAEs	2 (2)	5 (5)
SAEs with fatal outcome	0	0
AEs leading to trial discontinuation	0	0
AEs leading to discontinuation of trial drug	3 (3)	2 (2)

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; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Studies 1602 and 1704

There were no deaths in pooled Studies 1602 and 1704.

7.6.2.3. Serious Adverse Events, Studies 1602 and 1704

The SAE of thrombocytosis, previously noted in the SAEs section of Study 1704 (Section 7.6.1.3), was the only SAE reported with a higher frequency in the efgartigimod arm compared to placebo in pooled Studies 1602 and 1704 (1% versus 0%, respectively) (Table 33).

Table 33. Serious Adverse Events, Safety Population, Study 1602 and 1704

Serious Adverse Event[1]	Efgartigimod (N=96) n (%)	Placebo (N=95) n (%)
Thrombocytosis	1 (1)	0

Source: Clinical Safety Reviewer
[1] Coded as MedDRA preferred term
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, Studies 1602 and 1704

No AEs led to trial or treatment discontinuation in Study 1602.

7.6.2.5. Treatment-Emergent Adverse Events, Studies 1602 and 1704

Pooled Studies 1602 and 1704 had similar findings of infections as the most frequently reported TEAEs by preferred term as compared to Study 1704. The following tables (Table 34 and Table 35) list TEAEs by preferred term and FDA MedDRA Query that occur with a frequency of at least 5% in the efgartigimod arm and higher than placebo in pooled Studies 1704 and 1602.

Table 34. Treatment-Emergent Adverse Events[1] of at Least 5% and With Higher Frequency in Treatment Arm Than Placebo, Phase 2 and 3 Safety Population, Studies 1602 and 1704

	Pooled[3]	
Treatment-Emergent Adverse Event	**Efgartigimod (N=96) n (%)**	**Placebo (N=95) n (%)**
Urinary tract infection	8 (8)	2 (2)
Upper respiratory tract infection	7 (7)	1 (1)
Myalgia	5 (5)	1 (1)

Source: Clinical data scientist Dr. Ling Cao provided table
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
[3] Pooled phase 2 and 3 population. Includes only AEs occurring in the first treatment cycle of Study 1704.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event

Table 35. FDA MedDRA Queries[1] Occurring at Higher Frequency in Treatment Arm Than Placebo, Phase 2 and 3 Safety Population, Studies 1602 and 1704

	Pooled[2]	
FDA MedDRA Query	**Efgartigimod (N=96) n (%)**	**Placebo (N=95) n (%)**
Headache FDA narrow	25 (26)	21 (22)
Procedural headache	4 (4)	1 (1)
Migraine	2 (2)	0
Headache	22 (23)	19 (20)
Premenstrual headache	0	1 (1)
Post-traumatic headache	0	1 (1)
Paresthesia FDA narrow	6 (6)	4 (4)
Hypoesthesia	0	0
Hyperesthesia	1 (1)	0
Hypoesthesia oral	2 (2)	0
Paresthesia	3 (3)	4 (4)
Hemorrhage FDA narrow	5 (5)	4 (4)
Hematoma	1 (1)	0
Menorrhagia	1 (1)	0
Contusion	3 (3)	2 (2)
Subcutaneous hematoma	0	1 (1)
Epistaxis	0	1 (1)

	Pooled[2]	
FDA MedDRA Query	Efgartigimod (N=96) n (%)	Placebo (N=95) n (%)
Vertigo FDA broad	5 (5)	4 (4)
Balance disorder	1 (1)	0
Vertigo	1 (1)	0
Dizziness	3 (3)	4 (4)

Source: Clinical data scientist Dr. Ling Cao provided table
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Pooled phase 2 and 3 population. Includes only AEs occurring in the first treatment cycle of Study 1704.
[3] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.2.6. Laboratory Findings, Studies 1602 and 1704

Change From Baseline

Laboratory findings showed a higher frequency of decreased lymphocyte count, increased potassium, decreased leukocyte count, low hemoglobin, increased monocyte/leukocyte ratio, and increased calcium in efgartigimod-treated subjects.

The reviewer did not identify any clinically significant changes in analyses of mean change from baseline because of small magnitudes of change or because of small sample sizes at visits towards the end of treatment cycles in pooled Studies 1602 and 1704.

Shift Analyses by CTCAE Grade Severity and by High, Low, and Abnormal Values

In pooled Studies 1602 and 1704, outlier analyses of laboratory values with a postbaseline CTCAE Grade 1 or higher severity, and incidence of at least 5% higher in the efgartigimod arm compared to placebo, were observed with decreased lymphocyte count, increased potassium, and decreased leukocyte count.

The laboratory abnormalities of decreased lymphocyte count, increased potassium, and decreased leukocyte count had similar maximum values between efgartigimod and placebo arms. The maximum lowest lymphocyte count in the efgartigimod arm was 0.2 x 10^3/uL compared to 0.3 x 10^3/uL on placebo (reference range 0.9 to 4.3 x 10^3/uL). The maximum highest potassium count in the efgartigimod arm was 6.0 mEq/L compared to 5.9 mEq/L on placebo (reference range 3.5 to 5.2 mEq/L). The maximum lowest leukocyte count in the efgartigimod arm was 2.6 x 10^9/L (reference range 3.8 to 10.7 x 10^3/uL) compared to 2.7 x 10^9/L on placebo (reference range 4.1 to 12.3 x 10^3/uL).

Table 36 shows the frequency of subjects with postbaseline laboratory abnormalities of CTCAE Grade 1 or higher severity and at least 5% higher frequency in the efgartigimod arm compared to placebo.

Table 36. Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade 1 Severity or Higher and With Frequency of at Least 5% Higher in the Efgartigimod Arm Compared to Placebo, Safety Population, Studies 1704 and 1602[1]

	Pooled	
Laboratory Analysis	Efgartigimod n/N (%)	Placebo n/N (%)
Decreased lymphocytes	23/81 (28)	12/84 (14)
Increased potassium	13/95 (14)	4/93 (4)
Decreased leukocyte count	9/92 (10)	4/90 (4)

Source: Clinical safety reviewer
[1] CTCAE grading scale used for toxicity grades where Grade 1 severity or higher for lymphocytes is <0.8/0.91/1.02 x 10^3/uL, potassium is >5.1/5.2 mEq/L, leukocytes is <3.8/4.1 x 10^3/uL.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects; n, number of subjects with abnormality

The laboratory abnormality of decreased neutrophils occurred at a higher frequency in the efgartigimod arm compared to placebo in pooled Studies 1602 and 1705 (5% versus 4%, respectively), although the difference between arms was smaller when compared to the difference seen in Study 1704 alone (13% in efgartigimod arm versus 6% on placebo).

Decreased lymphocytes was the only laboratory parameter of CTCAE Grade 3 or higher severity (from a Grade 0 baseline) with higher frequency in the efgartigimod arm compared to placebo in pooled Studies 1704 and 1602, occurring in five subjects in the efgartigimod arm (6%) compared to one subject on placebo (1%).

In pooled Studies 1602 and 1704, outlier analyses with shifts in frequency of at least 5% higher in the efgartigimod arm compared to placebo occurred with hemoglobin shift to low, monocyte/leukocyte percentage shift to high, and calcium shift to high.

For hemoglobin, the lowest hemoglobin value was 6.3 g/dL (occurring at Week 2 and 4) (reference range 11.6 to 16.4 g/dL). The greatest decrease from baseline was 2.3 g/dL (occurring at Week 5). Only one subject experienced postbaseline hemoglobin values of less than 7 g/dL in pooled Studies 1704 and 1602 (Subject (b) (6)). This subject also reported the nonserious adverse events of worsening anemia, menorrhagia, myalgia, and rash within 2 weeks of the lab values.

For the monocyte/leukocyte ratio, the maximum ratio was similar between the efgartigimod and placebo arms (15% versus 17%, respectively).

For calcium, the greatest increase from baseline was 2.3 mg/dL (occurring at Week 5) and the greatest calcium value was 11.1 mg/dL (occurring at Week 11) (reference range of 8.3 to 10.6 mg/dL).

Table 37 shows laboratory abnormalities with shift from normal to worst postbaseline value and frequency of at least 5% higher in the efgartigimod arm in pooled Studies 1602 and 1704.

Table 37. Laboratory Abnormalities With Shift to High, Low, and Abnormal With a Frequency of at least 5% Higher in the Efgartigimod Arm Compared to Placebo, Safety Population, Studies 1704 and 1602[1]

	Pooled	
Laboratory Analysis	Efgartigimod n/N (%)	Placebo n/N (%)
Hemoglobin shift to low	16/81 (20)	9/87 (10)
Monocytes/leukocytes shift to high	11/88 (13)	4/82 (5)
Calcium shift to high	8/93 (9)	3/95 (3)

Source: Clinical safety reviewer
[1] Shift to high, low, and abnormal category in worst postbaseline value in subjects with a normal baseline value. The reviewer created this table using the 1704 ADLB2 dataset, baseline reference range indicator = normal, analysis reference range indicator = high, low, and abnormal, analysis visit = worst postbaseline visit ANRIND, analysis toxicity grade = missing.
Abbreviations: N, number of subjects; n, number of subjects with abnormality

TEAEs Related to Laboratory Findings

No TEAEs related to laboratory findings had frequency of 5% or greater in the efgartigimod arm in pooled Studies 1602 and 1704.

Hepatic-Related Events

The reviewer did not identify a safety signal for hepatic-related events in an analysis of maximum postbaseline liver enzyme values, hepatic-related adverse events, or Hy's law cases in pooled Studies 1704 and 1602.

No subjects in Study 1602 had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal, alkaline phosphatase (ALP) greater than 1.5 times the upper limit of normal, or bilirubin (BILI) greater than two times the upper limit of normal.

No subjects met Hy's law case criteria in Study 1602.

7.6.3. Safety Findings and Concerns, Studies 1704, 1602, and 1705

7.6.3.1. Overall Adverse Event Summary, Studies 1704, 1602, and 1705

At the time of the 90-Day Safety Update, five deaths had been reported in the long-term extension Study 1705. A role for efgartigimod in the events with fatal outcome could not be ruled out in two of the cases as the deaths occurred in the setting of infection, which was among the most frequently reported adverse events in clinical trials. Potential contributory factors for infections existed in both cases. In the remaining cases, the reviewer did not identify a role for efgartigimod. A higher frequency of subjects reporting at least one SAE was observed in pooled Studies 1704, 1602, and 1705 compared to Study 1704 alone (14% versus 5%, respectively). The higher frequency is likely in part because of longer follow-up in the long-term extension Study 1705. Myasthenia gravis, malignancy, and pneumonia were the most frequently reported SAEs. In pooled Studies 1704, 1602, and 1705, the incidence of a subject experiencing at least one TEAE was similar compared to Study 1704 alone (83% versus 77%, respectively). The most frequently reported TEAEs in pooled Studies 1704, 1602, and 1705 were related to headache, nasopharyngitis, and diarrhea.

Table 38 shows an overview of TEAEs in pooled Studies 1704, 1602, and 1705 after the 90-Day Safety Update.

Table 38. Overview of Treatment-Emergent Adverse Events, All Efgartigimod-Treated Trial Safety Population, After 90-Day Safety Update, Studies 1704, 1602, and 1705

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

7.6.3.2. Deaths, Studies 1704, 1602, and 1705

After the 90-Day Safety Update, a total of five deaths had been reported in the long-term extension Study 1705. Two deaths occurred in the setting of infection and a role for efgartigimod in the events could not be ruled out. In both cases, subjects had additional potential contributing factors for events related to infection.

Overall, the reviewer notes that the mortality rate in pooled Studies 1704, 1602, and 1705 was similar to mortality rates of subjects with myasthenia gravis in published cohort studies. Published cohort studies of subjects with myasthenia gravis note annual mortality rates of up to 23 to 26 deaths per 1,000 subjects with myasthenia gravis (Christensen et al. 1998; Hansen et al. 2016; Santos et al. 2016). The mortality rate observed in the pooled Studies 1704, 1602, and 1705 was 30.5 deaths per 1,000 subjects (5 deaths/164 person-years) and is similar to rates observed in these published studies.

Table 39 shows the incidence of death after the 90-Day Safety Update in pooled Studies 1704, 1602, and 1705.

Table 39. Deaths in Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

Deaths	Efgartigimod (N=162) n (%)
Total deaths	5 (3)
Acute myocardial infarction	1 (1)
Death	1 (1)
Lung neoplasm malignant	1 (1)
Myasthenia gravis crisis	1 (1)
Septic shock	1 (1)

Source: Clinical safety reviewer
Abbreviations: N, number of subjects in group; n, number of deaths

For the five SAEs with fatal outcome, the reviewer identified underlying risk factors that were likely contributory to the fatal outcomes. Table 40 lists AEs with fatal outcomes and potential contributory factors.

Table 40. Deaths Across the Clinical Program

Subject ID	Age, Sex	AE Listed as Cause of Death	Trial Day for AE Onset	Potential Contributory Factors
(b) (6)	55M	Acute myocardial infarction	242	Coronary artery disease
	79M	Myasthenia gravis crisis	230	Aspiration pneumonia, pneumonia Escherichia
	66F	Lung neoplasm malignant	356	History of squamous cell carcinoma
	72F	Death	258	Coronary artery disease, ischemic cardiomyopathy, cardiomegaly, hypertension
	62M	Septic Shock	519	COVID-19 pneumonia, acute respiratory failure, urinary tract infection, rheumatoid arthritis on immunosuppressive medications (prednisone, azathioprine)

Source: Safety reviewer
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; M, male; F, female

The reviewer summarizes three of the five deaths here. In two deaths, a role for efgartigimod in the events could not be ruled out as the deaths occurred in the setting of infection, which was among the most frequently reported AEs in clinical trials (septic shock in Subject (b) (6) and myasthenia gravis crisis in Subject (b) (6)). In the remaining case, the cause of death was unclear (death in Subject (b) (6)).

Septic Shock, COVID-19 Pneumonia, Urinary Tract Infection, Acute Respiratory Failure, Subject (b) (6):

62-year-old male with myasthenia gravis, obesity, hypertension, peripheral venous disease, rheumatoid arthritis, and atrial fibrillation was hospitalized on Day 485 for the SAE of COVID-19 pneumonia and developed acute respiratory failure, UTI, and septic shock leading to death. The subject developed acute respiratory failure the day following hospitalization and tested positive for SARS CoV-2. A high-resolution computed tomography showed interstitial pneumonitis affecting 70% of the lung parenchyma. IgG levels were reportedly within normal range on Day 485 (quantitative value not reported). Six days prior to hospitalization, the IgG level was 5850 mg/L (representing a 29% decrease from baseline in Study 1704).[5] The most recent leukocyte, neutrophil, and lymphocyte counts in Study 1705 were normal, occurring on Day 479. The most recent dose of efgartigimod had been 35 days before the hospitalization. The subject had received 24 doses of efgartigimod prior to the event. Concomitant medications

[5] The most recent laboratory assessments were provided by the Applicant in a response dated October 12, 2021, to an information request dated October 8, 2021. In an information response dated January 4, 2021, to an information request dated December 29, 2020, the Applicant noted that a reference range for pharmacodynamic analyses of IgG levels was not established and that pharmacodynamic analyses were based on change from baseline on treatment rather than on changes from a reference range.

included azathioprine, pyridostigmine, prednisone, diosmin plus hesperidin, digoxin, apixaban, furosemide, spironolactone, and omeprazole. Efgartigimod was withdrawn due to the SAE of COVID-19 pneumonia. The subject was intubated and had multiple unsuccessful attempts to be extubated over the following month. On Day 518, he developed circulatory system instability and was diagnosed with a UTI and septic shock. He was treated with intravenous antibiotics, corticosteroids, norepinephrine, and vasopressin. The outcome of septic shock was reported as fatal.

The 90-Day Safety Update included two updates to the narrative: the SAE of COVID-19 was updated to the preferred term COVID-19 pneumonia and the SAEs of UTI and acute respiratory failure were added.

Reviewer's comment*: A role for efgartigimod in the SAEs of septic shock, COVID-19 pneumonia, and UTI cannot be ruled out as infections were among the most frequently reported adverse events in Study 1704 and pooled Studies 1704 and 1602. Confounding factors for the events of septic shock, COVID-19 pneumonia, and UTI include concomitant immunosuppressive medication use with azathioprine and prednisone, whose labels contain warnings for risk of serious infection (Imuran 2018; Prednisone 2018). Additionally, the subject's prolonged intubated status was potentially contributory in the development of UTI. A role for efgartigimod in the event of acute respiratory failure cannot be confirmed as the event of COVID-19 pneumonia was likely contributory.*

Myasthenia Gravis Crisis, Aspiration Pneumonia, Escherichia Pneumonia, Shock, Stupor, Subject (b) (6)

79-year-old male with myasthenia gravis was hospitalized for the SAEs of myasthenia gravis crisis, aspiration pneumonia, and Escherichia pneumonia on Day 231 and died from myasthenia gravis crisis on Day 254. The SAEs of myasthenia gravis, aspiration pneumonia, and Escherichia pneumonia were all reported as starting on Day 254. The subject had received 8 doses of efgartigimod in Study 1704 and 4 doses in Study 1705, with the most recent dose occurring 54 days prior to the hospitalization (Day 177). Several days prior to hospitalization, the subject was reported to have had difficulty swallowing, worsening shortness of breath, fever, and cough with excess sputum production. Concomitant medications included pyridostigmine bromide, ethyl-2-bromoisovalerate/menta/piperita oil/phenobarbital, and oxymetazoline. His most recent IgG level, 25 days prior to hospitalization (Day 206), was 6080 mg/L (43% below his baseline value in Study 1704) and was higher than his nadir of 3590 mg/L (66% below baseline), which occurred on Day 177). Twenty-five days before the hospitalization, the neutrophil count had been normal at 4.73 x 10^9/L (reference range 1.96 to 7.23 x 10^9/L), the lymphocyte count had been normal at 1.93 x 10^9/L (reference range 0.8 to 3 x 10^9/L), and the white blood cell count had been normal at 7.11 x 10^9/L (reference range 3.8 to 10.7 x 10^9/L). Two days after admission, the SAEs of stupor and shock were also reported. On Day 242, acute respiratory distress syndrome, brain edema, chronic bronchitis, coagulopathy, encephalopathy, pericarditis, and pleural effusion were reported. Treatment included intubation, IV antibiotics, steroids, and plasmapheresis. He experienced a decline in his clinical status, including cerebral hypoxemia, cerebral edema, and dislocation of the brainstem. Death occurred on Day 254 with the primary cause assessed as myasthenia gravis crisis. No autopsy was performed.

***Reviewer's comment**: The event of myasthenia gravis was reported on the same day as the events of aspiration and Escherichia pneumonia. A role for efgartigimod in the SAEs of aspiration pneumonia and Escherichia pneumonia cannot be ruled out as respiratory tract infections were among the most frequently reported adverse event in Study 1704 and pooled Studies 1704 and 1602. Potential contributory factors for the development of aspiration pneumonia and Escherichia pneumonia included the subject's baseline symptoms of choking with swallowing and intermittent slurring/nasal speech (noted on the Myasthenia Gravis- Activities of Daily Living assessment), which are risk factors for the development of pneumonia. The reviewer did not identify a role for efgartigimod in the event of myasthenia gravis crisis as the event was separated from the drug by approximately 8 weeks.*

Death, Subject (b) (6)

72-year-old female with history of myasthenia gravis, coronary artery disease, ischemic cardiomyopathy, cardiomegaly, chronic obstructive pulmonary disease, hypertension, history of UTIs, pulmonary embolism, hypokalemia, drug sensitivity to codeine, hydrocodone, and olmesartan was found unconscious at home and pronounced dead on Day 259. An autopsy showed patent coronary stents in her left anterior descending coronary artery and patent circumflex and posterior descending coronary arteries. Cardiomegaly was noted on the autopsy as well as thymoma. Other recent illnesses preceding her death included a diagnosis of colovesical fistula 3 months beforehand, with interval colostomy placement, and the development of nausea 9 days before death, which was treated with calcium chloride/potassium chloride/sodium lactate, ondansetron, lidocaine hydrochloride, and magnesium hydroxide/simethicone. Concomitant medications included cholecalciferol, vitamin B12, iodine, and fish oil. She had received 4 doses of efgartigimod in Study 1704 and 9 doses of efgartigimod in Study 1705, with the most recent dose occurring 4 days before the event of death.

***Reviewer's comment**: Although the autopsy did not identify the cause of death, the reviewer considered the subject to be at risk for arrhythmia, given the findings of cardiomegaly on autopsy and the subject's history of ischemic cardiomyopathy. The reviewer did not identify a role for efgartigimod in the event of death given these potential contributing factors.*

The 90-Day Safety Update included updates to the narratives of three subjects with SAEs with fatal outcome (Subjects (b) (6)). The updates to the narratives in subjects with fatal outcome did not change my initial assessment of the role of efgartigimod in these events. The reader is referred to the Appendix 17.3 for a summary of these updates.

7.6.3.3. Serious Adverse Events, Studies 1704, 1602, and 1705

Myasthenia gravis, malignancy, and pneumonia were the most frequently reported SAEs in pooled Studies 1704, 1602, and 1705. The following tables (Table 41 and Table 42) show SAEs reported in efgartigimod-treated subjects in pooled Studies 1704, 1602, and 1705 by preferred term and FDA MedDRA Query.

Table 41. Serious Adverse Events, Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

Serious Adverse Event[1]	Efgartigimod (N=162) n (%)
Myasthenia gravis/myasthenia gravis crisis	6 (4)
COVID-19 pneumonia	2 (1)
Acute myocardial infarction	1 (1)
Acute respiratory failure	1 (1)
Adenocarcinoma of colon	1 (1)
Anemia	1 (1)
Arrhythmia	1 (1)
Bladder neck obstruction	1 (1)
Cardiac failure congestive	1 (1)
Colectomy	1 (1)
COVID-19	1 (1)
Death	1 (1)
Depression	1 (1)
Diarrhea	1 (1)
Dysentery	1 (1)
Irritable bowel syndrome	1 (1)
Lung neoplasm malignant	1 (1)
Pancreatic carcinoma	1 (1)
Pneumonia	1 (1)
Pneumonia aspiration	1 (1)
Pneumonia Escherichia	1 (1)
Prostate cancer	1 (1)
Rectal adenocarcinoma	1 (1)
Retinal detachment	1 (1)
Septic shock	1 (1)
Shock	1 (1)
Spinal compression fracture	1 (1)
Squamous cell carcinoma of the vulva	1 (1)
Stupor	1 (1)
Thrombocytosis	1 (1)
Urinary tract infection	1 (1)

Source: Clinical safety reviewer
[1] Coded as MedDRA preferred term
Abbreviations: COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

Table 42. FDA MedDRA Queries[1] of SAEs, Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

FDA MedDRA Query[3]	Efgartigimod (N=162) n (%)
Malignancy FDA narrow	5 (3)
Adenocarcinoma of colon	1 (1)
Lung neoplasm malignant	1 (1)
Pancreatic carcinoma	1 (1)
Prostate cancer	1 (1)
Rectal adenocarcinoma	1 (1)
Squamous cell carcinoma of the vulva	1 (1)
Pneumonia FDA narrow	4 (2)
COVID-19 pneumonia	2 (1)
Pneumonia	1 (1)
Pneumonia aspiration	1 (1)
Pneumonia Escherichia	1 (1)

Source: Clinical safety reviewer
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

There were no SAEs of aplastic anemia, acute pancreatitis, agranulocytosis, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, sudden death/Torsade's, or thrombotic thrombocytopenia purpura in the myasthenia gravis trials.

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, Studies 1704, 1602, and 1705

Trial Discontinuation

Adverse events led to trial discontinuation in five subjects (3%) in pooled Studies 1704, 1602, and 1705.

One of the five subjects who discontinued because of an adverse event was from Study 1704 and is discussed in the section on Dropouts and/or Discontinuations for Study 1704 (Subject (b) (6), rectal adenocarcinoma, Section 7.6.1.4).

The remaining four subjects who discontinued because of an adverse event were from Study 1705 and reported the following preferred terms: spinal compression fracture, myalgia/headache, myasthenia gravis, and COVID-19 pneumonia/myasthenia gravis. The reviewer did not identify a role for efgartigimod in three of four cases because of contributory factors such as past medical history or because of a lack of temporal association. These cases are discussed in Section 17.3.2 of the Appendix (spinal compression fracture, Subject (b) (6); myasthenia gravis, Subject (b) (6); and COVID-19 pneumonia/myasthenia gravis, Subject (b) (6)). The reviewer did not rule out a role for efgartigimod in the fourth trial discontinuation case from Study 1705 and summarizes the case here.

Headache, Myalgia (Subject [redacted])

42-year-old female with past medical history of myasthenia gravis, headache, hypertension, anemia, and hypothyroidism who reported a mild headache and myalgia 2 days after the 14th and 15th efgartigimod dose (Days 202 and 208). The subject was treated with paracetamol both times and the adverse event was considered to be resolved/resolving or recovered/recovering. Concomitant medications included pyridostigmine, prednisone, levothyroxine, ferroglycine sulfate complex, pantoprazole, ergocalciferol, and hydrochlorothiazide-telmisartan. In Study 1704, the subject had reported a mild headache 19 days after the 8th dose of efgartigimod (Day 112). The subject discontinued from Study 1705 because of the headache and myalgia.

***Reviewer's comment**: A role for efgartigimod cannot be ruled out given the temporal association with event onset and drug administration. The subject's history of headache is a potential contributory factor in the case.*

Treatment Discontinuation

In pooled Studies 1704, 1602, and 1705, adverse events leading to treatment discontinuation were reported in 7% of subjects (11/162). Eight of the 11 subjects were from Study 1705. Four of the eight subjects from Study 1705 are discussed above under Trial Discontinuations (spinal compression fracture, Subject [redacted]; myasthenia gravis, Subject [redacted]; COVID-19 pneumonia/myasthenia gravis, Subject [redacted]; and headache/myalgia, Subject [redacted]). The remaining four cases are discussed in the Deaths section of the section of pooled Studies 1704, 1602, and 1705 (acute myocardial infarction, Subject [redacted]; COVID-19 pneumonia, Subject [redacted]; death, Subject [redacted]; and lung neoplasm malignant, Subject [redacted]; Section 7.6.3.2).

Myasthenia gravis, COVID-19 pneumonia, and malignancy were the most frequently reported AEs leading to treatment discontinuation in pooled Studies 1602, 1704, and 1705. The following tables (Table 43 and Table 44) show adverse events leading to treatment discontinuation in pooled Studies 1704, 1602, and 1705 by preferred term and FDA MedDRA Query.

Table 43. Adverse Events Leading to Treatment Discontinuation, Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

Adverse Event[1]	Efgartigimod (N=162) n (%)
Myasthenia gravis	3 (2)
COVID-19 pneumonia	2 (1)
Acute myocardial infarction	1 (1)
Balance disorder	1 (1)
Death	1 (1)
Facial paresis	1 (1)
Headache	1 (1)
Lung neoplasm malignant	1 (1)
Myalgia	1 (1)
Rash	1 (1)
Rectal adenocarcinoma	1 (1)
Restless legs syndrome	1 (1)
Spinal compression fracture	1 (1)
Thrombocytosis	1 (1)

Source: Clinical safety reviewer, AEs leading to treatment discontinuation in subjects who withdrew from the trial due to an adverse event.
[1] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of subjects in group; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory Activities

Table 44. FDA MedDRA Queries[1] of Adverse Events Leading to Treatment Discontinuation, Safety Population, After the 90-Day Safety Update, Study 1704, 1602, and 1705

FDA MedDRA Query[2]	Efgartigimod (N=162) n (%)
Malignancy FDA narrow	2 (1)
Lung neoplasm malignant	1 (1)
Rectal adenocarcinoma	1 (1)

Source: Clinical data scientist Dr. Ling Cao
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.3.5. Treatment-Emergent Adverse Events, Studies 1704, 1602, and 1705

The most frequently reported TEAEs by FDA MedDRA Query in pooled Studies 1704, 1602, and 1705 included headache, nasopharyngitis, and diarrhea. These TEAEs had similar frequency in pooled Studies 1602, 1704, and 1705 compared to Study 1704 (difference no greater than 5%).

Table 45. Treatment-Emergent Adverse Events[1] Occurring With at Least 7% Frequency, Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

Preferred Term[2]	Efgartigimod (N=162) n (%)
Urinary tract infection	15 (9)
Nausea	13 (8)
Upper respiratory tract infection	12 (7)

Source: Clinical safety reviewer
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory Activities

Table 46. FDA MedDRA Queries[1] Occurring With at Least 7% Frequency, Safety Population, After the 90-Day Safety Update, Studies 1704, 1602, and 1705

FDA MedDRA Query[3]	Efgartigimod (N=162) n (%)
Headache FDA narrow	57 (35)
Headache	53 (33)
Migraine	7 (4)
Procedural headache	7 (4)
Migraine with aura	1 (1)
Migraine without aura	1 (1)
Nasopharyngitis FDA narrow	29 (18)
Nasopharyngitis	23 (14)
Pharyngitis	4 (2)
Pharyngitis streptococcal	2 (1)
Rhinitis	1 (1)
Viral pharyngitis	1 (1)
Diarrhea FDA narrow	19 (12)
Diarrhea	17 (10)
Post procedural diarrhea	2 (1)
Dysentery	1 (1)
Arthralgia FDA broad	13 (8)
Arthralgia	7 (4)
Neck pain	3 (2)
Musculoskeletal stiffness	2 (1)
Joint stiffness	1 (1)
Spinal pain	1 (1)
Dizziness FDA narrow	13 (8)
Dizziness	9 (6)
Vertigo	3 (2)
Balance disorder	2 (1)

FDA MedDRA Query[3]	Efgartigimod (N=162) n (%)
Hemorrhage FDA narrow	11 (7)
Contusion	5 (3)
Hematochezia	2 (1)
Hematoma	1 (1)
Injection site bruising	1 (1)
Menorrhagia	1 (1)
Metrorrhagia	1 (1)
Subcutaneous hematoma	1 (1)

Source: Clinical safety reviewer
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.6.3.6. Laboratory Findings, Studies 1704, 1602, and 1705

Laboratory findings showed laboratory abnormalities with highest frequency were increased triglycerides, decreased lymphocytes, and increased cholesterol.

Change from Baseline

The reviewer did not identify any clinically significant changes in analyses of mean change from baseline because of small magnitudes of change or because of small sample sizes at visits towards the end of treatment cycles in pooled Studies 1704, 1602, and 1705.

Shift Analyses by CTCAE Grade Severity and by High, Low, and Abnormal Values

In pooled Studies 1704, 1602, and 1705, the most frequent postbaseline laboratory abnormalities of CTCAE Grade 1 or higher severity were increased triglycerides (52%), decreased lymphocytes (31%), and increased cholesterol (27%). Refer to the Dyslipidemia section of this review (Section 7.7.3) for further discussion of the topic of dyslipidemia. The following tables (Table 47 and Table 48) show postbaseline laboratory parameters with frequency of 10% or higher of CTCAE Grade 1 or higher severity and the frequency of subjects with postbaseline laboratory parameters of CTCAE Grade 3 or higher severity from Grade 0 at baseline in pooled Studies 1704, 1602, and 1705.

Table 47. Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade 1 Severity or Higher With a Frequency of at Least 10%, Safety Population, Studies 1704, 1602, and 1705[1]

Laboratory Analysis	Efgartigimod n/N (%)
Increased triglycerides[2]	53/101 (52)
Decreased lymphocytes	42/137 (31)
Increased cholesterol[2]	33/124 (27)
Increased aspartate aminotransferase	34/155 (22)
Increased alanine aminotransferase	32/154 (21)
Decreased leukocytes	23/155 (15)
Decreased neutrophils	24/160 (15)
Decreased glucose	22/153 (14)
Increased potassium	22/160 (14)
Increased sodium	20/161 (12)
Increased activated partial thromboplastin time	16/161 (10)
Increased Gamma Glutamyl Transferase	15/149 (10)

Source: Clinical safety reviewer
[1] CTCAE grading scale used for toxicity grades where Grade 1 or higher severity for triglycerides are > or = to 144 to 326 mg/dL, lymphocytes are <0.8/0.91/1.02 x 10^3/uL, cholesterol is >198 to 352 mg/dL, aspartate aminotransferase is >31 to 37 U/L, alanine aminotransferase is >32 to 43 U/L, neutrophils are <1.96/2.03 x 10^3/uL, glucose is <70 to 83 mg/dL, leukocytes is <3.8/4.1 x 10^3/uL, potassium is >5.1/5.2 mEq/L, sodium is >145/147 mEq/L, activated partial thromboplastin time is >32.5/39.9 sec,
[2] Denominators adjusted to include pooled Studies 1704 and 1705 only as cholesterol-related labs were not measured in Study 1602. The reviewer created this table using the Pb2 ADLB2 90-Day Safety dataset, Analysis visit = worst postbaseline ATOXGR, baseline toxicity grade =0, analysis toxicity grade =1, 2, 3, or 4.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects; n, number of subjects with abnormality

Table 48. Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade 3 Severity or Higher, Safety Population, Studies 1704, 1602, and 1705[1]

Laboratory Analysis	Efgartigimod n/N (%)
Decreased lymphocytes	8/137 (5)
Decreased neutrophils	1/160 (1)
Increased sodium	2/161 (1)

Source: Clinical safety reviewer
[1] CTCAE grading scale used for toxicity grades.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects; n, number of subjects with abnormality

Adverse Events in Subjects With Laboratory Parameters With CTCAE Grade 3 or Higher Severity

The reviewer evaluated adverse events occurring in efgartigimod-treated subjects with laboratory parameters of CTCAE Grade 3 or higher severity from any grade at baseline (decreased leukocytes, decreased lymphocytes, decreased neutrophils, increased sodium, increased triglycerides, and increased cholesterol).

Overall, the reviewer did not find an association between laboratory parameters with CTCAE Grade 3 or 4 severity and serious adverse events.

No subjects with CTCAE Grade 3 or higher laboratory parameters of decreased leukocytes, decrease lymphocytes, or decreased neutrophils reported a serious adverse event within the SOC of Infection and Infestations.

One subject had CTCAE Grade 3 severity of increased cholesterol and increased triglycerides and was diagnosed with cardiovascular disease on cardiac catheterization while in the study

(Subject [redacted]). Potential contributory factors for the development of cardiovascular disease in this subject included the subject's history of hyperlipidemia, obstructive sleep apnea, and left and right bundle branch blocks.

The reviewer notes four serious adverse events that occurred in four subjects with CTCAE Grade 3 or higher severity laboratory parameters. Two of the four subjects had a postbaseline CTCAE Grade 3 severity of increased triglyceride levels and reported the SAE of myasthenia gravis (Subjects [redacted]). The remaining two subjects had a postbaseline CTCAE Grade 3 severity of decreased lymphocytes and reported the SAEs of spinal compression fracture (Subject [redacted]) and congestive heart failure (Subject [redacted]).

TEAEs Related to Laboratory Findings

No TEAEs related to laboratory findings had frequency of 5% or greater in the efgartigimod arm in pooled Studies 1704, 1602, and 1705.

Hepatic-Related Events

The reviewer did not identify a safety signal for hepatic-related events in an analysis of maximum postbaseline liver enzyme values, hepatic-related adverse events, or Hy's law cases in pooled Studies 1704, 1602, and 1705.

Pooled Studies 1602, 1704, and 1705 had similar frequency of subjects with maximum postbaseline liver enzyme values (ALT or AST greater than three times the upper limit of normal, ALP greater than 1.5 times the upper limit of normal, or BILI greater than two times the upper limit of normal) compared to Study 1704 (difference no greater than 3%).

No subjects met Hy's law case criteria in Study 1705.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Infections

Issue

TEAEs related to infection were among the most frequently reported adverse events in Study 1704.

Background

The topic of infections was of special interest as the Applicant's proposed label notes that infections were among the most frequently reported AEs in clinical trials. Additionally, efgartigimod results in a reduction of circulating IgG and reduced IgG levels have been associated with increased risk of infection (Agarwal and Cunningham-Rundles 2007; Furst 2009; Driessen et al. 2013).

Assessment

Tables and graphs submitted by the Applicant and summarized in the Summary of Clinical Pharmacology Studies in this BLA submission were reviewed. For pharmacodynamic analyses of IgG levels, the Applicant notes that a reference range for IgG levels was not established as pharmacodynamic analyses were based on change from an individual's baseline rather than comparison with a reference range.[6] The reviewer notes that the level of IgG reduction at which point an individual is potentially at higher risk for infection varies by individual. Refer to Section 17.6 for a summary of publications related to that topic.

Treatment with efgartigimod resulted in lowering of IgG levels. In Study 1704, the mean maximal reduction in total IgG in efgartigimod-treated subjects in the overall population in Cycle 1 occurred at Week 4 (after four infusions of efgartigimod) and was 3129 mg/L, representing a 62% decrease from mean baseline values.[7] By Week 12, IgG levels had increased to within 10% of mean baseline values. No significant changes from mean baseline IgG were observed in subjects on placebo. In Study 1602, the mean maximal reduction in total IgG in efgartigimod-treated subjects occurred at Week 4 and was 2980 mg/L, representing a 71% decrease from mean baseline values. No significant changes in IgG levels were observed in subjects on placebo. In Study 1705, the mean maximal total IgG reduction in Cycle 1 of the overall population occurred at Week 3 and was 3130 mg/L, representing a 57% decrease from mean baseline values.[8] By Week 11, IgG levels had increased to within 10% of baseline values.

In Study 1704, a higher frequency of TEAEs belonging to the SOC of Infections and Infestations was observed in the efgartigimod 10 mg/kg arm compared to placebo (46% versus 37%, respectively). The most frequently reported TEAEs were upper respiratory tract infection, UTI, and bronchitis. Table 49 shows TEAEs belonging to the SOC of Infections and Infestations in Study 1704 with higher frequency in the efgartigimod arm compared to placebo.

[6] Noted in an information response dated January 4, 2021, to an information request dated December 29, 2020.
[7] The reviewer reviewed data submitted by the Applicant in Tables 14.2.8.1.2 and 14.2.8.2.2. of the report body for Study 1704.
[8] The reviewer reviewed data submitted by the Applicant in Tables 14.2.3.1.2 and 14.2.3.2.2. of the report body interim 1 for Study 1705. IgG levels were not measured at Week 4 in Study 1705.

Table 49. TEAEs Belonging to the SOC of Infections and Infestations With Higher Frequency in Efgartigimod 10 mg/kg Arm Compared to Placebo, Study 1704

Preferred Term	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Subjects with at least one TEAE belonging to the SOC of infections and infestations	39 (46)	31 (37)
Upper respiratory tract infection	9 (11)	4 (5)
Urinary tract infection	8 (10)	4 (5)
Bronchitis	5 (6)	2 (2)
Ear infection	2 (2)	0
Sinusitis	2 (2)	0
Gastroenteritis	1 (1)	0
Gingivitis	1 (1)	0
Nail bed infection	1 (1)	0
Oral herpes	1 (1)	0
Pharyngitis	1 (1)	0
Pneumonia	1 (1)	0
Rotavirus infection	1 (1)	0
Viral pharyngitis	1 (1)	0
Viral tracheitis	1 (1)	0
Vulvovaginal mycotic infection	1 (1)	0

Source: This table was created by the reviewer using 1704 ADAE dataset
Treatment-emergent analysis flag = Y; Body System or Organ Class = Infections and Infestations; Group by Unique Subject Identifier, Actual Treatment and Dictionary-derived term.
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Pooled Studies 1602 and 1704 showed similar findings of a higher frequency of TEAEs belonging to the SOC Infections and Infestations in the efgartigimod 10 mg/kg arm compared to placebo (33% versus 25%, respectively). Similar to Study 1704 alone, the most frequently reported AEs included upper respiratory tract infection, UTI, and bronchitis. Refer to Section 17.8 for a list of TEAEs belonging to the SOC of Infections and Infestations from pooled Studies 1602 and 1704.

In pooled Studies 1704, 1602, and 1705, a higher frequency of subjects reported a TEAE belonging to the SOC of Infections and Infestations compared to Study 1704 (54% versus 46%, respectively). The higher frequency is, in part, likely due to a longer follow-up in the long-term extension Study 1705. Similar to Study 1704, upper respiratory tract infection, UTI, and bronchitis were among the most frequently reported TEAEs. Nasopharyngitis was also among the most frequently reported TEAEs in pooled Studies 1704, 1602, and 1705, but was not among the most frequently reported adverse events in Study 1704 as the frequency in the efgartigimod 10 mg/kg arm did not exceed placebo. Refer to Section 17.8 for a list of TEAEs belonging to the SOC of Infections and Infestations from pooled Studies 1704, 1602, and 1705. Most of the TEAEs related to infection were mild or moderate in severity (45% CTCAE Grade 1, 48% CTCAE Grade 2).

In Study 1704, no subjects reported SAEs belonging to the SOC of Infections and Infestations in the efgartigimod arm compared to one subject on placebo (1%). In pooled Studies 1704 and 1602, no SAEs belonging to the SOC of Infections and Infestations were reported in any subjects. In pooled Studies 1704, 1602, and 1705, SAEs belonging to the SOC Infections and Infestations were reported in 4% of subjects.

Across the clinical program, nine SAEs related to the SOC of Infections and Infestations were reported in seven subjects after the 90-Day Safety Update. Preferred terms for the nine SAEs included COVID-19 pneumonia (n=2) and pneumonia (n=2); COVID-19, dysentery, pneumonia Escherichia, septic shock, and urinary tract infection each occurred only once.

The reviewer notes that a role for efgartigimod in the SAEs related to infection cannot be ruled out because infections were among the most frequently reported adverse events in efgartigimod-treated subjects in clinical trials and occurred more frequently in efgartigimod than in placebo-treated subjects. Six of the seven SAEs occurred in the long-term extension Study 1705 and the seventh occurred in Study 1603. Two of the seven subjects with SAEs related to infection had fatal outcomes (septic shock/COVID-19 Pneumonia/urinary tract infection/acute respiratory failure, Subject (b) (6); and myasthenia gravis crisis/aspiration pneumonia/Escherichia pneumonia/shock, Subject (b) (6)). In both cases, other factors were potentially contributory to the events of infection, including concomitant immunosuppressive medication use and baseline symptoms of dysphagia in an event of aspiration pneumonia. Refer to Section 7.6.3.2 for narratives of these AEs with fatal outcome.

The remaining five subjects with SAEs related to infection had potential contributory factors for the AEs of infection, including concomitant immunosuppressive medication use and underlying risk factors such as past medical history. For a review of these narratives, refer to Section 17.3.2. In the seven subjects with SAEs related to infection, the most recent laboratory analyses (within 25 days prior to the event onset) did not identify low lymphocyte, leukocyte, or neutrophil counts.[9] The most recent IgG levels ranged between 3110 mg/L and 7590 mg/L and were between a 3% increase and a 61% decrease compared to baseline IgG values in Study 1704.

In Trials 1704 and 1602, no AEs related to infection led to trial or treatment discontinuation. In Study 1705, two subjects reported adverse events related to infection, both reporting the preferred term of COVID-19 pneumonia leading to treatment discontinuation (Subjects (b) (6)). One of the two subjects withdrew from the trial because of the adverse event (Subject (b) (6)). In both cases, the subjects were on immunosuppressive medications (including azathioprine, mycophenolate mofetil, and prednisone), which were potential contributory factors to the development of infection.

One efgartigimod-treated subject (1%) in Study 1704 interrupted treatment because of an adverse event related to infection (UTI) compared to no subjects on placebo. In Study 1602, no AEs related to infection were reported to lead to treatment interruption. In Study 1705, 12 subjects interrupted treatment because of an adverse event related to infection. Preferred terms included respiratory tract infection/respiratory tract infection viral/viral upper respiratory tract infection (n=4), nasopharyngitis (n=2), and pharyngitis/pharyngitis streptococcal (n=2); COVID-19, dysentery, herpes zoster, pneumonia, urinary tract infection, and viral infection each occurred only once.

[9] The most recent laboratory assessments were provided by the Applicant in a response dated October 12, 2021, to an information request dated October 8, 2021.

The reviewer notes that five efgartigimod-treated subjects in Study 1704 were hepatitis B carriers. None of the subjects experienced AEs related to acute hepatitis in Study 1704 or 1705. No subjects in Studies 1602, 1704, or 1705 had a history of latent tuberculosis.

A higher frequency of low leukocytes, low lymphocytes, and low neutrophils was reported in efgartigimod-treated subjects compared to placebo. In Study 1704, a higher frequency of efgartigimod-treated subjects compared to placebo had decreased leukocyte counts (12% versus 5%), decreased lymphocyte counts (28% versus 19%), and decreased neutrophils (13% versus 6%). Similar findings were observed in pooled Studies 1704 and 1602. Refer to the sections on laboratory findings for Study 1704, pooled Studies 1704 and 1602, and pooled Studies 1704, 1602, and 1705 for further details (Sections 7.6.1.6, 7.6.2.6, and 7.6.3.6).

Compared to all subjects in pooled Studies 1704, 1602, and 1705, a higher frequency of infection was reported in subjects with low lymphocyte counts (62% versus 54%) and low neutrophil counts (63% versus 54%). Analyses of the frequency of infection by low leukocyte, lymphocyte, and neutrophil count were limited by the small number of subjects in each arm (<30), and a role for low leukocyte, lymphocyte, and neutrophil counts in the AEs of infection cannot be concluded. Table 50 shows the frequency of infections in efgartigimod-treated subjects who experienced low leukocyte, lymphocyte, or neutrophil count at any point in time in pooled Studies 1704, 1602, and 1705 at the 90-Day Safety Update.

Table 50. Frequency of TEAEs Related to Infection by Low Leukocyte, Lymphocyte, and Neutrophil Count Status at Any Point in Time, at the 90-Day Safety Update, Pooled Studies 1704, 1602, and 1705

Population	Number of Subjects	Number of Events	Number of Events/ Number of Subjects (%)[1]
All subjects	162	88	54
Low leukocyte	23	12	52
Low lymphocyte	42	26	62
Low neutrophil	24	15	63

Source: This table was created by the reviewer using ISS Pb2 ADAE dataset 90-Day safety update
Treatment-emergent analysis flag = Y; Primary System Organ Class = Infections and Infestations; subjects level flags = low leukocyte, lymphocyte, and neutrophils counts. Low leukocyte count defined as count <3.8 to 4.1 x 10^3/uL, low lymphocyte count defined as <0.8 to 1.02 x 10^3/uL, low neutrophils count defined as count <1.96 to 2.03 x 10^3/uL
[1] For subjects with multiple events within a laboratory category, the event is counted only once.
Abbreviations: TEAE, treatment-emergent adverse event

Conclusion

Overall, the reviewer notes that treatment with efgartigimod results in reduction in IgG levels. TEAEs belonging to the SOC of Infections and Infestations were among the most frequently reported TEAEs in Study 1704. The most frequent preferred terms included upper respiratory tract infection, UTI, and bronchitis. Similar findings were observed with pooled Studies 1602 and 1704 and Studies 1704, 1602, and 1705. No SAEs belonging to the SOC of Infections and Infestations were reported in efgartigimod-treated subjects in Studies 1704 or 1602. In pooled Studies 1704, 1602, and 1705, 4% of subjects reported an SAE belonging to the SOC of Infections and Infestations. Higher frequencies of decreased lymphocyte, leukocyte, and neutrophil counts were observed in efgartigimod-treated subjects compared to placebo in Study 1704 and pooled Studies 1704 and 1602.

The reviewer recommends a Warnings and Precautions statement for Infections in labeling based the pharmacology of the drug, given the drug's IgG-lowering effects and associations with low

lymphocyte, leukocyte, and neutrophil counts. As per the Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October 2011),

> *The Warnings and Precautions section should include serious or otherwise clinically significant adverse reactions that are anticipated to occur with a drug if it appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug.*

Additionally, because there is uncertainty regarding the potential for more serious outcomes in the postmarketing period where subjects are monitored less frequently than in a clinical trial setting, a Warnings and Precautions statement may mitigate potentially serious outcomes of infections by alerting providers to the risk.

It is unknown whether treatment with efgartigimod increases the risk of reactivation of hepatitis B or latent tuberculosis (TB). Five efgartigimod-treated hepatitis B carriers in Study 1704 did not develop acute hepatitis in Study 1704 or 1705. No subjects reported a history of latent TB in Studies 1602 or 1704/1705. Given the small number of hepatitis B carriers in the trials and an absence of subjects with a history of latent TB, a conclusion regarding the risk of reactivation of hepatitis B or latent TB with efgartigimod therapy cannot be drawn. The reviewer recommends enhanced pharmacovigilance for reactivation of hepatitis B and latent TB.

7.7.2. Hypoalbuminemia

Issue

Hypoalbuminemia

Background

Albumin levels were of special interest because the Fc receptor is involved in maintaining serum albumin circulation and the proposed mechanism of action of efgartigimod is to bind to the neonatal Fc receptor.

Assessment

Mean albumin levels did not decrease below baseline by more than 0.4 g/dL in Study 1704, pooled Studies 1704 and 1602, and pooled Studies 1704, 1602, and 1705. No subjects in Study 1704, pooled Studies 1602 and 1704, or pooled Studies 1704, 1602, and 1705 had decreased albumin levels of CTCAE Grade 1 severity or higher.

Conclusion

The reviewer did not identify a safety signal for hypoalbuminemia with treatment with efgartigimod.

7.7.3. Dyslipidemia

Issue

Dyslipidemia

Background

Cholesterol levels were of special interest as LDL levels were reported to increase by 60% in a phase 2 study after 12 weeks of therapy with IMVT-1401, a human monoclonal antibody targeting the neonatal Fc receptor developed for thyroid eye disease (Mast 2021). In addition, increased triglycerides and cholesterol were among the most frequently occurring laboratory abnormalities in pooled Studies 1704 and 1705.

In this section, the efgartigimod-treated group for lipid analyses includes only data from pooled Studies 1704 and 1705 as lipids were not collected in Study 1602. LDL and high-density lipoprotein (HDL) changes were measured by categorical shifts to high and low. Shifts in total cholesterol and triglyceride levels were measured by CTCAE grade severity.

Assessment

LDL

The maximum mean increase in LDL by visit was small in Study 1704 and pooled Studies 1704 and 1705 (less than 11 mg/dL).

In Study 1704, a lower frequency of efgartigimod-treated subjects had a shift in LDL from normal to high compared to placebo (6% versus 14%, respectively). A higher frequency of efgartigimod-treated subjects compared to placebo-treated subjects had a shift in LDL from normal to low (36% versus 31%, respectively).

In pooled Studies 1704 and 1705, a higher percentage of subjects had a shift in LDL from normal to low compared to normal to high (35% versus 13%, respectively).

Total Cholesterol

The maximum mean increase in total cholesterol by visit was small in Study 1704 and pooled Studies 1704 and 1705 (less than 14 mg/dL).

In Study 1704, efgartigimod and placebo arms had the same frequency of shifts to a higher CTCAE severity grade for increased cholesterol (17%). No efgartigimod-treated subject had increased total cholesterol of CTCAE Grade 3 or higher.

In pooled Studies 1704 and 1705, 28% of subjects had an increase in CTCAE grade from baseline for elevated cholesterol. One percent had an increase in total cholesterol to CTCAE Grade 3 or higher.

Triglycerides

The maximum mean increases in triglycerides in Study 1704 occurred in one subject (increase of 205 mg/dL from baseline in Cycle 3, Week 10). Excluding the one visit, the maximum mean increase in triglycerides was 52.2 mg/dL (occurring in a group of six subjects in Cycle 3, Week

1). The reviewer notes that larger increases in mean triglycerides from baseline occurred in later treatment cycles and are likely in part because of increased variability due to smaller numbers of subjects in later treatment cycles in Study 1704. In pooled Studies 1704 and 1705, the maximum mean increase in triglycerides was 16 mg/dL.

In Study 1704, a higher frequency of subjects in the efgartigimod arm compared to placebo had shifts to higher CTCAE grade severity postbaseline for elevated triglycerides (41% versus 34%, respectively). A similar percentage of subjects in the efgartigimod arm had an increase in triglycerides to CTCAE Grade 3 or higher severity compared to placebo (2% versus 1%, respectively).

In pooled Studies 1704 and 1705, 49% had an increase in CTCAE grade severity with elevated triglycerides. One percent had an increase in triglycerides to CTCAE Grade 3 or 4.

HDL

The maximum mean increase in HDL by visit was small in Study 1704 and pooled Studies 1704 and 1705 (less than 7 mg/dL).

In Study 1704, a similar frequency of efgartigimod-treated subjects compared to placebo-treated subjects had a shift in HDL from normal to high (25% versus 22%, respectively) and a shift in HDL from normal to low (1% versus 2%, respectively).

In pooled Studies 1704 and 1705, a higher percentage of subjects had a shift in HDL from normal to high compared to normal to low (38% versus 3%, respectively).

Conclusion

The reviewer did not identify a safety signal for elevated LDL or other lipids in subjects treated with efgartigimod.

7.7.4. Hypersensitivity Reactions

Issue

Hypersensitivity reactions

Background

The topic of hypersensitivity reactions was of special interest as the Applicant's proposed label includes infusion reactions as a Warnings and Precautions statement.

Assessment

The protocols in Trials 1704 and 1705 required that subjects remain on site for at least 1 hour following the end of the infusion. The protocol in Study 1602 required subjects to remain on site for at least 2 hours following the end of the infusion.

The Applicant performed a search of TEAEs occurring within 48 hours of an infusion belonging to the broad category of Standardised MedDRA Queries (SMQs) for Hypersensitivity, Anaphylactic Reaction, and Extravasation Events, and to a customized query of extravasation events excluding implants.

The reviewer also analyzed TEAEs occurring within 48 hours of an infusion and belonging to the narrow SMQ categories for Hypersensitivity, Anaphylactic Reaction, and Extravasation Events.

No serious AEs or AEs leading to treatment discontinuation occurred within 48 hours of infusion with efgartigimod and belonged to the broad or narrow SMQs for Hypersensitivity, Anaphylactic Reaction, and Extravasation Events in Studies 1704, 1602, or 1705.

In Study 1704, there was not an excess of TEAEs related to hypersensitivity, anaphylactic reaction, and extravasation events in the efgartigimod arm compared to placebo. Table 51 shows the frequency of TEAEs related to hypersensitivity, anaphylactic reaction, and extravasation events by SMQs in Study 1704.

Table 51. Frequency of TEAEs Related to Hypersensitivity, Anaphylactic Reaction, and Extravasation Events, Study 1704

SMQs	Scope	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Hypersensitivity	Narrow	2 (2)	2 (2)
	Broad	1 (1)	2 (2)
Anaphylactic reaction	Narrow	0	0
	Broad	2 (2)	5 (6)
Extravasation events	Narrow	0	1 (1)
	Broad	0	1 (1)

Source: Safety Reviewer
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event; SMQ, Standardised MedDRA Query; TEAE, treatment-emergent adverse event

In Study 1704, two subjects experienced nonserious TEAEs belonging to the broad SMQ Anaphylactic Reaction that were likely hypersensitivity reactions. Bilateral upper eyelid swelling was reported in a 45-year-old female subject with a history of seasonal allergies within 3 hours of the first dose of efgartigimod (Subject (b) (6)). The symptom resolved within 2 hours without the addition of concomitant medications. The subject received 11 additional doses and did not have reoccurrence of symptoms. A second subject, a 48-year-old female, reported generalized body itching within 90 minutes of the first dose of efgartigimod (Subject (b) (6)). The symptom resolved within 2 hours without the administration of concomitant medications. The subject received 27 additional doses and did not have recurrence of the AE.

The reviewer notes that the events of eyelid swelling appear to be consistent with angioedema based on the description of the AE. Both cases are likely hypersensitivity reactions given the occurrence within 2 hours of an infusion and may be non-IgE-mediated hypersensitivity reactions given absence of previous exposure to efgartigimod.

In pooled Studies 1704 and 1602, the frequency of TEAEs related to hypersensitivity, anaphylactic reaction, and extravasation events in the efgartigimod arm did not exceed placebo by more than 1%.

In pooled Studies 1704, 1602, and 1705, the frequency of TEAEs related to hypersensitivity, anaphylactic reaction, and extravasation events by preferred term did not exceed 4%. In Study 1705, one subject experienced the event of acute respiratory failure along with the SAEs of myasthenia gravis crisis and pneumonia and the TEAE of hypertension (Subject (b) (6)

1 (b) (6)). The reviewer did not identify a role for efgartigimod in the event of acute respiratory failure because of likely contributory factors of pneumonia and myasthenia gravis crisis. Further details of the case are discussed in Section 17.3.2. In Study 1705, another subject experienced the nonserious AE of dyspnea and oropharyngeal discomfort within 4 hours of an infusion (Subject (b) (6)). The reviewer summarizes the narrative below.[10]

Dyspnea, Oropharyngeal Discomfort, and Somnolence, Subject (b) (6)

A 55-year-old female with history of myasthenia gravis, asthma, seasonal allergy, obesity, essential tremor, hyperlipidemia, and hypothyroidism reported the nonserious TEAEs of dyspnea (verbatim term: difficulty breathing), oropharyngeal discomfort (verbatim term: pounding sensation in throat), and somnolence (verbatim term: drowsiness) on the same day as her 20th infusion. The subject developed a sensation of inhaling dust, worsening hand tremors, cold sensation in the hands, a feeling of being "foggy," and a headache within 60 minutes after completing the infusion of efgartigimod on Day 162. She denied feeling chest tightness or throat tightness. Vital signs at the time of symptoms included a blood pressure of 117/61 mm Hg and a heart rate of 87 beats per minute. The subject was given diphenhydramine 25 mg intravenously and ibuprofen 600 mg orally. Within 2 hours, her respiratory symptoms had resolved and the TEAE of somnolence was reported as resolved the same day. The TEAE of oropharyngeal discomfort was reported as resolved the following day. The subject was given diphenhydramine 25 mg orally twice daily for 5 days as treatment for the dyspnea.

Four days later (Day 166), the subject presented to the emergency department with episodic shortness of breath. Her blood pressure was 127/80 mm Hg and heart rate was 67 beats per minute. The subject was evaluated for influenza and underwent an electrocardiogram, which was reported as being within normal limits. The subject was treated with hydroxyzine and cetirizine and discharged after approximately 3 hours of observation. On that day, the TEAE of allergic transfusion reaction was reported (verbatim term: possible allergic reaction to infusion, CTCAE Toxicity Grade 2).

Two days later (Day 168), the subject saw her primary care provider for dyspnea, palpitations, tremors, and anxiety. She was given diagnoses of dyslipidemia, anxiety, hypothyroidism, and allergic state; prescribed Buspar; and advised to continue taking antihistamines.

Eight days later (Day 176), she saw another primary care provider and was diagnosed with nasal and sinus inflammation. The provider recommended that the subject receive an intramuscular dose of corticosteroids followed by a tapered dose of oral steroids. The subject declined the steroids because of concern of violating study protocol and being discontinued from the study. She continued treatment with hydroxyzine and cetirizine.

On Day 212, she reported the TEAEs of palpitations (Grade 2) and nausea (Grade 1) while she was receiving her 24th infusion. Treatment was interrupted due to these TEAEs and the outcome of both events were reported as resolved on the same day. She went on to receive an additional 20 infusions without occurrence of TEAEs.

[10] Information also included in the Applicant's response dated August 18, 2021, to an information request dated August 16, 2021 and response dated August 25, 2021, to an information request dated August 24, 2021.

Concomitant medications included fluticasone propionate, salmeterol xinafoate, primidone, levothyroxine, calcium, cholecalciferol, gabapentin, vitamins, meloxicam, ibuprofen, loratadine, atorvastatin, and vitamin B12.

Prior to the AEs of dyspnea, oropharyngeal discomfort, and somnolence, AEs reported by the subject on the same day of infusion included nonserious headache within 30 minutes of the first and second dose of efgartigimod (Days 1 and 8 of Study 1704, respectively), generalized pain approximately 2 hours after the third dose (Day 15 of Study 1704), and chills 1 hour after the 18th infusion of efgartigimod (Day 147 of Study 1705).

This reviewer notes that the AEs of dyspnea and oropharyngeal discomfort likely represent an IgE-mediated hypersensitivity reaction given onset within 4 hours of the infusion and previous exposures to efgartigimod.

The most frequent TEAE related to hypersensitivity, anaphylactic reaction, and extravasation events in pooled Studies 1704, 1602, and 1705 was rash (frequency of 4% for pooled preferred terms: rash (n=3), rash maculo-papular (n=2), rash macular, and dermatitis). Rashes were noted in subjects up to 3 weeks after the last dose of efgartigimod. Verbatim terms included left arm dermatitis, rash on the neck, rash on the chest, rash maculo-papular on the chest and arms, rash maculo-papular on the chest, macular truncal rash, and maculopapular rash on the back. Onset of the AEs ranged from cycles 1 through 10 of treatment with efgartigimod. Three of the six subjects with rash had a second episode of rash that occurred within 2 days of an infusion (Subjects (b) (6)). Medications administered for the rashes included cetirizine and diphenhydramine. The duration of the AE ranged between 3 to >368 days. All cases of rash were CTCAE Grade 1 except for one case which was CTCAE Grade 2. An excess of TEAEs related to rash in the efgartigimod arm compared to placebo was not observed in Study 1704 and pooled Studies 1704 and 1602.

Other preferred terms belonging to the broad or narrow SMQs Hypersensitivity, Anaphylactic Reaction, and Extravasation Events SMQs in pooled Studies 1704, 1602, and 1705, included cough (n=2), infusion site pain, and sensation of foreign body.

The preferred term procedural headache was reported at higher frequency in efgartigimod-treated subjects than in placebo-treated subjects in Study 1704 (5% versus 1%, respectively). The AEs occurred within 6 to 48 hours after dosing. Verbatim terms for efgartigimod-treated subjects included “mild headache at day of last infusion,” “headache after IP administration,” “headaches occurring after each infusion and lasting until the next day,” and “headache at top left of head…occurs right after infusion.” Most of the headaches were mild and did not require additional treatment. Subjects had received between one and five doses of efgartigimod prior to reporting the headaches. In pooled Studies 1704 and 1602, procedural headache was reported in 4% of efgartigimod-treated subjects compared to 1% on placebo. Procedural headache was reported in 4% of efgartigimod-treated subjects in pooled Studies 1704, 1602, and 1705.

The reviewer notes that headache could potentially represent a hypersensitivity reaction or could be an adverse event occurring around the time of when efgartigimod is at maximum concentration.

Conclusion

Hypersensitivity reactions, including rash, dyspnea, and angioedema, were observed in efgartigimod-treated subjects in Trials 1704, 1602, and 1705. The reviewer did not identify any SAEs or cases of anaphylaxis related to efgartigimod. Some cases were likely IgE-mediated as they occurred after multiple doses of efgartigimod. No cases led to treatment discontinuation. There was not an imbalance of TEAEs related to hypersensitivity, anaphylactic reaction, and extravasation events in Study 1704 or pooled Studies 1704 and 1602.

The reviewer recommends that hypersensitivity reactions be added as a Warnings and Precautions statement. The Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October 2011) recommends that otherwise clinically significant adverse reactions be included in Warnings and Precautions statement. Hypersensitivity reactions are potentially serious as they potentially result in serious outcomes such as hypotension, anaphylaxis, or death. A Warnings and Precautions statement will help alert providers to this risk.

7.7.5. AEs in the Acetylcholine Receptor Antibody Seronegative Population

Issue

Frequency of AEs in the AChR-Ab seronegative population

Background

The frequency of adverse events in the AChR-Ab seronegative population was of special interest as the efficacy of efgartigimod in this population was of special interest. Refer to Section 6.3.1 for further details.

Assessment

The reviewer compared the frequency of TEAEs, SAEs, TEAEs causing discontinuation, and severity of AEs in the AChR-Ab seronegative population to the overall safety population in Study 1704. In addition, because AEs related to infection were among the most frequently reported AEs across the clinical trials and one of the key issues relevant to the evaluation of risk, the reviewer also evaluated their frequency in the seronegative population compared to the overall population.

There were 19 subjects with AChR-Ab seronegative status in Study 1704, representing 23% of the overall safety population. A similar frequency of TEAEs, SAEs, TEAEs causing discontinuation, and AEs related to infection was observed in the AChR-Ab seronegative population compared to the overall population. The reviewer notes that because of the low number of subjects in the AChR-Ab seronegative population, a conclusion regarding the role of seronegative status on the frequency of AEs cannot be made. Table 52 shows the frequency of AEs in the AChR-Ab seronegative population and the overall population in Study 1704.

Table 52. Frequency of AEs in the AChR-Ab Seronegative Population and the Overall Population, Study 1704

	AChR-Ab Seronegative		Overall	
Parameters	EFG (N=19) n (%)	PBO (N=19) n (%)	EFG (N=84) n (%)	PBO (N=83) n (%)
Any TEAE	16 (84)	16 (84)	65 (77)	70 (84)
Any TEAE related to infection	10 (53)	9 (47)	39 (46)	31 (37)
Any SAE	1 (5)	1 (5)	4 (5)	7 (8)
Any SAE related to infection	0	0	0	1 (1)
Any TEAE causing treatment discontinuation	1 (5)	0	3 (4)	3 (4)
Any CTCAE Grade 1 TEAE	15 (79)	13 (68)	56 (67)	58 (70)
Any CTCAE Grade 2 TEAE	16 (84)	16 (84)	38 (45)	37 (45)
Any CTCAE Grade 3 TEAE	3 (16)	1 (5)	9 (11)	8 (10)

Source: safety reviewer
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EFG, efgartigimod; N, number of subjects in treatment group; n, number of subjects with given characteristic; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Conclusion

Because of the low number of subjects in the AChR-Ab seronegative population, a conclusion regarding the role of seronegative status on the frequency of AEs cannot be made.

7.7.6. Immunizations

Issue

Immunizations in labeling

Background

Treatment with efgartigimod is associated with reductions in IgG levels, decreased leukocyte, lymphocyte, and neutrophil counts, and increased frequency of infections. Refer to Section 7.7.1 for further details.

The Applicant submitted the following Warnings and Precautions statement on immunizations in their proposed label.

Immunization with vaccines during VYVGART therapy has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are unknown. (b) (4)

vaccination with live or live attenuated vaccines is not recommended. (b) (4)

The Division consulted the Center for Biologics Evaluation and Research (CBER) for recommendations regarding timing of immunization in the setting of treatment with efgartigimod.

Assessment

In a CBER consult response dated to August 5, 2021, Dr. Soumya Chatterjee noted that the Applicant had not submitted any vaccine co-administration studies with efgartigimod. Refer to Section 17.13 for the complete CBER consult response.

(b) (4)

Dr. Chatterjee notes that vaccine utilization guidelines by professional medical societies and advisory committees generally recommend that nonlive vaccinations be administered preferably before starting immune-modulating therapies and that subjects undergoing treatment with biologic immune-modulating drugs should not receive live vaccinations.

(b) (4)

CBER proposes the following revisions to the Applicant's proposed language

> *Immunization with vaccines during efgartigimod (brand name: VYVGART) therapy has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with any vaccine is unknown. Administer all age-appropriate vaccines according to immunization guidelines before initiation of treatment with VYVGART.*

(b) (4)

Because treatment with efgartigimod is associated with reductions in IgG levels, decreased leukocyte, lymphocyte, and neutrophil counts, and increased frequency of infection, the reviewer agrees that the safety of immunization with live and live-attenuated vaccines and the response to immunization with any vaccine is unknown, and that patients should be vaccinated with age-appropriate vaccinations according to immunization guidelines prior to starting therapy with efgartigimod.

Conclusion

Because efgartigimod is associated with reductions in IgG levels, decreased leukocyte, lymphocyte, and neutrophil counts, and increased frequency of infection, a Warnings and Precautions statement in labeling can help highlight that the safety of immunization with live and live-attenuated vaccines and the response to immunization with any vaccine is unknown, and that patients should be vaccinated with age-appropriate vaccinations according to immunization guidelines prior to starting therapy with efgartigimod. (b) (4)

(b) (4)

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

No dedicated hepatic impairment study was performed. The Applicant recommends that no dose adjustment is needed in patients with hepatic impairment.

The Applicant evaluated the effect of hepatic impairment biomarkers on the exposure of efgartigimod using population PK analysis and concluded that none of these biomarkers affected the exposure of efgartigimod (Figure 14). An information request was sent to the Applicant on November 2, 2021, to report and evaluate the hepatic impairment using the Child-Pugh criteria. In their response (received on November 3, 2021) the Applicant noted that although subjects with hepatic impairment were allowed enrollment in Study 1704, all subjects enrolled were classified as Child-Pugh class A and no subjects with hepatic impairment classified as Child-Pugh class B or C severity enrolled. Therefore, because of limited data in other categories, hepatic impairment based on Child-Pugh on the impact of efgartigimod PK was not evaluated in population PK analyses.

However, efgartigimod is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids. As a result, hepatic impairment is not expected to affect efgartigimod PK and therefore, the review team agrees with the Applicant's recommendation that no dose adjustment is needed in patients with hepatic impairment.

Renal Impairment

No dedicated renal impairment study was performed. The Applicant noted that mild renal impairment did not affect the overall safety profile of efgartigimod, and therefore recommends that no dose adjustment is needed in such patients. Further, they noted that there are insufficient data on impact of moderate renal impairment, and no data on the impact of severe renal impairment on efgartigimod PK. (b) (4)

Although renal elimination is a minor excretion pathway for efgartigimod (<0.1% dose excreted in urine unchanged) based on PK data from single-ascending dose Study 1501, population PK analysis suggested a relative area under the concentration-time curve change of 1.22 (90%CI: 1.13, 1.30) in subjects with mild renal impairment relative to subjects with normal renal function which is not clinically significant. Figure 18 and Figure 19 show the efgartigimod concentration time course from subjects with normal renal function (estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73m^2, N=58), mild renal function (eGFR ≥60 to <90 ml/min/1.73m^2, N=23), and moderate renal function (eGFR ≥30 to <60 ml/min/1.73m^2, N=3). Table 53 shows the summary of efgartigimod concentration measured predose (within 1 hour prior to start of infusion) and after the end of 1-hour infusion (within 1 hour after end of infusion) on visit 4.

The data were either limited (only three subjects) or unavailable in subjects with moderate and severe renal impairment respectively, to evaluate the impact of renal impairment on efgartigimod PK in such subjects.

Table 53. Summary Statistics of Efgartigimod Plasma Concentrations at Four Weekly Infusions of Efgartigimod IV 10 mg/kg in Subjects With gMG Stratified by Renal Function

	Mean (SD)		
Parameter (Units)	**Normal Renal Function (N=56)**	**Mild Renal Impairment (N=22)**	**Moderate Renal Impairment (N=3)**
C_{max} (ng/mL)	222.5 (73.0)	236.6 (72.5)	246(65)
C_{trough} (ng/mL)	11.04 (4.6)	16.4 (6.2)	21.3(14.1)

Source: Reviewer's Analysis
Note: Subject (b) (6) with normal renal function and Subject (b) (6) w/mild renal impairment were excluded from analysis due to missing dose.
Abbreviations: C_{max}, maximum plasma concentration; C_{trough}, plasma concentration reached prior to next dose; gMG, generalized myasthenia gravis; IV, intravenous; N, number of subjects in group; SD, standard deviation

Overall, the review team agrees with the Applicant's proposal. Renal impairment is not expected to significantly affect efgartigimod PK in patients with mild renal impairment, and therefore no dose adjustment is needed. However, the data are too few in moderate and severe renal impairment, and therefore no dose adjustment recommendations can be provided in such subjects. (b) (4) . The review team recommended safety monitoring for all patients receiving efgartigimod; (b) (4)

Other Intrinsic Factors

The population PK analyses indicated that efgartigimod PK was not affected by age, sex, or race. The Applicant recommends that dose adjustments are not warranted based on these factors (Section 14.5), and the review team agrees with that recommendation.

A bodyweight-based dosing was followed throughout the clinical development program of efgartigimod. In phase 2 Study 1602 and phase 3 Study 1704, subjects received 4 weekly doses of 10 mg/kg Q1W (one treatment cycle), and specifically subjects who weighed >120 kg received a fixed dose of 1200 mg Q1W*4. The Applicant's proposed dosing instructions are consistent with the dosing regimens evaluated in phase 2 and 3 studies. In addition, the PK/PD analysis confirmed that a fixed dose for patients with body weight >120 kg will have comparable reduction in total IgG levels.

8.2. Extrinsic Factors

8.2.1. Drug Interactions

8.2.1.1. Effect of Other Drugs on Efgartigimod

Efgartigimod is a human IgG1 Fc-fragment and is expected to be catabolized by degradation to small peptides and individual amino acids, which are expected to be excreted or recycled via pathways in the same manner as endogenous IgG in humans. 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 vitro pharmacology studies revealed that while the wild type Fc fragment did not show binding at a pH of 7.4, efgartigimod Kd (dissociation constant) was 9nM for human FcRn, likely indicating efficient FcRn blockage as binding of efgartigimod already occurs at the cell surface without the competition of endogenous IgG that is unable to bind FcRn at a neutral pH. Further, efgartigimod was reported to bind with increased affinity, i.e., 100-fold higher at a pH of 6.0 compared to that of wild-type human IgG1 Fc.

After binding to FcRn, a portion of efgartigimod is hypothesized to be subject to lysosomal degradation alone or in complex with FcRn. The percentage of potential loss of FcRn-complexed efgartigimod has not been investigated; hence the rate of its catabolism, though unknown, is likely the predominant pathway in disposition of efgartigimod. Therefore, other therapeutic proteins are unlikely to alter the binding of efgartigimod to the FcRn receptor.

8.2.1.2. Effect of Efgartigimod on Other Drugs

Efgartigimod binds to FcRn and may decrease the concentrations of therapies that binds to human FcRn (i.e., immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass), is likely to result in reduced effectiveness of these moieties.

The Applicant noted that approximately 2 weeks after the last of 4 weekly infusions of efgartigimod IV 10 mg/kg, total IgG levels start to increase, while the efgartigimod concentrations dropped to less than 2% of its maximum concentration observed at the end of the infusion (3.24 µg/mL versus 253 µg/mL in cycle 1 of Study 1704). Based on these results, the Applicant states that 2 weeks after the last infusion, IgG catabolism is no longer meaningfully affected by efgartigimod and has returned to its normal rate. The Applicant expects that a clinically relevant effect on PK and PD of therapeutic moieties noted above is unlikely to occur when they are given 2 weeks or later after the last efgartigimod infusion. (b) (4)

The review team acknowledges that the total IgG levels start to increase approximately 2 weeks after the last of four weekly infusions of efgartigimod IV 10 mg/kg. (b) (4)

In addition, the proposed dosing regimen of efgartigimod is 10 mg/kg administered once weekly for 4 weeks, constituting one treatment cycle. Administration of subsequent treatment cycles is based on clinical examination. Based on the data in Studies 1704 and 1705 presented in Section 6.3.2, most myasthenia gravis patients who respond to an initial treatment with efgartigimod would be expected to need retreatment approximately a few weeks after the last efgartigimod

infusion. (b) (4)

The review team recommends close monitoring for reduced effectiveness of therapeutic moieties that bind to human FcRn, such as those noted above, when concomitant use is necessary. When long-term use of such medications is essential for patient care, the review team recommends stopping efgartigimod use and using alternative gMG medications.

Albumin disposition is known to be mediated by FcRn receptor. The review team analyzed the impact of efgartigimod on albumin levels and do not expect any clinical relevance for altering the disposition of highly protein-bound drugs.

Immunizations

Immunization with vaccines during efgartigimod therapy has not been studied. The Applicant notes that the safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are unknown (b) (4) the Applicant states that vaccination with live or live attenuated vaccines is not recommended, (b) (4)

Unlike the effect of efgartigimod on other therapeutic moieties such as those listed above, the effect of efgartigimod on vaccines is fundamentally and mechanistically different in that all kinds of vaccines are antigens and are highly unlikely to be affected directly by efgartigimod. Instead, the vaccines elicit immunological responses by triggering the body to produce antibodies, which are known to be affected by efgartigimod administration. (b) (4)

8.3. Plans for Pediatric Drug Development

Not applicable. Efgartigimod was granted orphan drug designation. Pediatric assessments are waived.

8.4. Pregnancy and Lactation

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 doses of 0, 30, and 100 mg/kg QD.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) has assessed BLA 761195 and has determined that the application meets all applicable standards to support the approval of efgartigimod manufactured by argenx BV. The data and information submitted in the application are adequate to support the conclusion that the manufacture of efgartigimod 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

The results of the clinical site inspections support the conclusion that the studies were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 20 for a summary of inspection findings and Section 23 for financial disclosures.

11. Advisory Committee Summary

Not applicable.

III. Appendices

12. Summary of Regulatory History

(b) (4)

Efgartigimod was primarily developed under IND 132953 submitted on March 17, 2017, for the treatment of MG. The IND contained a non-United States phase 1 clinical study report in healthy volunteers. The initial IND proposed a phase 2 clinical study in subjects with MG. The study was allowed to proceed on April 14, 2017. Efgartigimod was granted orphan drug designation on September 20, 2017, for the treatment of MG.

At the end-of-phase 2 (EOP2) meeting, discussions focused on labeling the intermittent dosing strategy and the pivotal phase 3 study design (minutes dated April 26, 2018). A chemistry, manufacturing, and controls (CMC)-only EOP2 meeting discussed the process validation plan and stability package (minutes dated May 30, 2018).

On April 11, 2018, the Sponsor submitted a preliminary breakthrough therapy designation request advice form. As discussed in a teleconference held on May 31, 2018, it was determined that it was premature to discuss a breakthrough therapy designation request since the Sponsor did not submit data demonstrating an improvement over available therapies for the treatment of MG.

Fast track designation was granted on February 18, 2020. Although there are two approved therapies for MG (pyridostigmine bromide and eculizumab), efgartigimod had potential to address an unmet medical need specifically to treat patients who are seronegative for acetylcholine receptor (AChR) antibodies. The phase 3 program was designed to assess an unmet need.

In the pre-biologics license application (BLA) meeting (minutes dated August 26, 2020), the Division agreed to the proposed size of the database and dosing frequency (i.e., 80 to 89 subjects with a follow-up of at least 12 months, with 45 to 50 of those subjects having received at least seven cycles of treatment). This data needed to be provided at the time of the BLA submission for the application to be considered complete. The Sponsor inquired about priority review which could not be determined at that time and would be determined at the time of BLA submission.

In an email on October 14, 2020, the Division agreed that the proposed safety database of 83 subjects with a follow-up of at least 12 months, and 43 subjects treated with seven or more cycles, as defined in the statistical analysis plan, with a follow-up of at least 12 months will be sufficient for submission of the BLA. Additionally, the Division notified the Sponsor in an email on July 30, 2020, that carcinogenicity studies are not needed. The CMC-only pre-BLA meeting discussed the Quality sections of the BLA submission (minutes dated August 14, 2020).

Consistent with FDA's Grant Rolling Review letter dated October 1, 2020, the BLA was submitted in three portions: Nonclinical section on October 22, 2020, Quality section on November 27, 2020, and Clinical section on December 17, 2020.

Because efgartigimod for the treatment of generalized myasthenia gravis (gMG) was granted orphan designation, the Applicant was exempted from the Pediatric Research Equity Act requirements. No written requests have been issued under Best Pharmaceuticals for Children Act.

The Applicant requested priority review in their BLA submission on December 17, 2020. The Division determined that the application did not appear to provide data to address an unmet need in gMG and granted a standard review.

The Applicant submitted a treatment protocol (expanded access protocol) to IND 132953 on February 12, 2021, entitled, "An Expanded Access Program for Efgartigimod Treatment in Patients with Generalized Myasthenia Gravis." The purpose of this treatment protocol was to provide availability of efgartigimod for patients with gMG during the review of the submitted BLA. The Study May Proceed letter was sent to the Applicant on March 12, 2021.

The proprietary name review request was submitted on December 18, 2020, and conditionally approved on March 17, 2021.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application

13.1.1. Pharmacology (Primary and Secondary)

Efgartigimod is a human IgG1-derived Fc fragment targeting the neonatal Fc receptor (FcRn). The product was engineered to increase affinity for the FcRn at neutral and acidic pH, (b) (4)

When bound to the FcRn, efgartigimod blocks binding of IgG and inhibits the FcRn-mediated recycling of IgG. Inhibition of this recycling process results in shorter half-life of plasma IgG and, thus, lower plasma IgG levels.

A series of in vitro studies were conducted to characterize the binding of efgartigimod. These studies demonstrated that ARGX-113 binds to FcRn of multiple species (rat, mouse, pig, dog, human, and monkey). FcRn binding of efgartigimod was compared to binding of a human wild-type IgG1Fc fragment. As summarized in the tables below, the affinity of efgartigimod for human and monkey FcRn were similar, affinity for rodent FcRn was significantly greater, and affinity for efgartigimod for rabbit FcRn was significantly lower.

Table 54. Affinity of Efgartigimod and Human Wild-Type IgG1 Fc Fragment to FcRn of Different Species as Determined With SPR

Species FcRn	pH	Dissociation constant (K_D±SD)	
		Human wild-type IgG1 Fc (nM)	efgartigimod (nM)
Mouse FcRn	7.4	No binding	0.64±0.11
	6.0	1.04±0.29	0.01±0.01
Rat FcRn	7.4	No binding	1.89±0.35
	6.0	7.54±0.93	0.53±0.11
Rabbit FcRn[a]	7.4	Low binding	301
	6.0	36.0	6.37
Pig FcRn	7.4	No binding	11.7±2.03
	6.0	1.76±0.61	0.35±0.05
Dog FcRn	7.4	No binding	1.74±0.19
	6.0	36.0±13.6	0.19±0.05
Cynomolgus monkey FcRn	7.4	No binding	14.5±2.77
	6.0	55.2±23.2	0.23±0.18
Human FcRn	7.4	No binding	8.59±1.35
	6.0	28.0±6.20	0.35±0.06

Source: Module 4.2.1.1, ARGX-NC-074, ARGX-NC-115
Fc=fragment, crystallized; FcRn=neonatal Fc receptor; IgG1=immunoglobulin G1; K_D=equilibrium dissociation constant; SD=standard deviation; SPR=surface plasmon resonance
[a] A different methodology was followed to determine rabbit FcRn affinity. Corresponding human FcRn affinities in this experiment were 8.63 nM (efgartigimod, pH 6.0), 31.0 nM (efgartigimod, pH 7.4), and 23.0 nM (wild-type Fc, pH 6.0).

(b) (4)

In all in vitro assays, efgartigimod bound with higher affinity at human FcRn at both acidic and neutral pH, compared to WT Fc fragment.

In vivo studies were conducted to characterize the pharmacodynamic (PD) activity of efgartigimod (i.e., reduction in plasma IgG levels) and the potential for efficacy in animal models of MG. The expected reduction in plasma IgG was observed across studies in all species tested. Specificity was demonstrated in multiple studies in which levels of plasma IgM or IgA were not affected after dosing with efgartigimod.

When administered IV to cynomolgus monkeys at a dose of 20 mg/kg (single dose or repeated dosing every 4 days), IgG levels were reduced approximately 55% after both single and repeated dosing. With repeated dosing, the reduction in IgG was similar to that observed after a single dose but was of longer duration. In a study comparing the PD of efgartigimod among species, dose-related reductions in IgG were observed in mouse (up to 66% at 2-100 mg/kg), rat (up to 48% at 2-100 mg/kg), and monkey (up to 55% at 0.2-200 mg/kg).

The potential efficacy of efgartigimod was investigated in multiple studies using passive transfer models of MG in rats. Treatment with ARGX-113 (IP at 1 mg/animal) resulted in reduced plasma IgG as well as improved grip strength and reduced disease scores relative to control.

Because FcRn also plays a role in albumin homeostasis, serum albumin was monitored in vivo after IV ARGX-113 dosing. Serum albumin was not affected in monkey but was slightly elevated (10-20%, not dose-related) in rat after 28 days of dosing.

13.1.2. Safety Pharmacology

A safety pharmacology study was conducted to assess CNS and respiratory systems. Cynomolgus monkeys received 5 weekly doses via 30-minute IV infusion at dose levels of 0, 10, 30, and 100 mg/kg. No CNS safety concerns were demonstrated. No drug-related effect on respiratory rate, the only respiratory parameter assessed, was observed.

Pharmacokinetics

Biological therapeutic products are metabolized by proteases and are not affected by liver microsomal enzymes. Metabolites are smaller peptides or amino acids and are either recycled into new proteins or are excreted in the urine.

The $t_{1/2}$ of efgartigimod in monkeys ranged from 8 hours at 2 mg/kg to 38 hours at 20 mg/kg IV. At 200 mg/kg, the $t_{1/2}$ of efgartigimod was approximately 21 hours, due to accelerated α-phase, which the sponsor attributed to rapid renal clearance of excess serum levels of the product above saturation. In toxicology studies, exposures appeared to increase slightly greater than dose proportionally. No significant difference in PK parameters between sexes was observed.

Human PK:

The intended clinical dose is 10 mg/kg via 1-hour IV infusion, weekly for 4 weeks.

Table 55. Summary of Efgartigimod PK Parameters-MAD (q7d Regimen)

	Part 2: Multiple Ascending Dose							
	10 mg/kg q7d N=6				25 mg/kg q7d* N=6			
PK parameter	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22
C_{max} (µg/mL)	195 (15.8)	202 (22.9)	237 (17.1)	204 (10.9)	535 (25.4)	393 (28.1)	407 (17.9)	485 (28.1)
t_{max} (h)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.1 (2.0-8.0)	2.0 (2.0-2.0)	2.0 (2.0-2.1)
C_{168h} (µg/mL)	8.02 (14.1)	10.2 (26.2)	10.2 (21.1)	NA	16.1 (33.3)	17.5 (20.9)	18.9 (24.1)	NA
AUC_{0-168h} (µg.h/mL)	5392 (11.5)	5936 (10.9)	6024 (9.01)	5612 (11.5)	12458 (25.0)	10315 (27.3)	10061 (19.6)	11152 (16.8)
R_{ac}	NA	1.10 (8.48)	1.12 (13.6)	1.04 (4.74)	NA	0.822 (12.4)	0.814 (14.5)	0.907 (12.9)

N=number of subjects, NA=not applicable, Values are arithmetic mean (CV%) except median (min-max) for t_{max} and geometric means (CV%) for R_{ac}
*For the q7d regimen at the dose 25 mg/kg, only the data from the Cohort 10 are summarized in this table.
Source: Table 14.2.2.2

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Table 56. Summary of Efgartigimod PK Parameters- Four Weekly Infusions 10 mg/kg, Study ARGX-113-1602

	Day 1	Day 8	Day 15	Day 22
C_{max} (µg/mL)	179 (31.9)	174 (19.5)	153 (22.1)	163 (26.1)
t_{max} (h)	2.4 (7.1)	2.4 (7.2)	2.4 (7.1)	2.4 (7.2)
C_{trough} (µg/mL)	7.27 (43.5)	9.89 (54.7)	10.05 (56.7)	10.9 (71.1)
AUC_{tau} (µg.h/mL)	8430 (37.3)	8755 (27.1)	8195 (32.2)	7856 (35.8)
R_{ac}	N/A	N/A	N/A	0.9360 (25.7)

NA=not applicable; Values are geometric mean (geometric CV%)

Source: CSR Study 1602

13.1.3. Toxicology

13.1.3.1. General Toxicology

The pivotal general toxicity studies were conducted in rat (28-day) and monkey (single dose, 28-day, and 26-week). All studies used IV administration. Liver and kidney were target organs in shorter term (28-day, dosing every other day) studies. In the 26-week study in monkey, longer dosing intervals (once per week) were used, and the liver and kidney toxicity were not observed.

Study Number: 32188

Title: Single Dose Toxicity Study of ARGX-113 by 2-hour Intravenous Infusion to Cynomolgus Monkeys

Cynomolgus monkeys received a single IV infusion at dose levels of 0, 10, 30, 50, or 100 mg/kg main-study animals were euthanized on study day (SD) 4, and recovery animals were euthanize**d on SD 29 after a 28-day recovery period. A slight reduction in body weight gain was observed from SD 1 to SD 15 in all dose groups (5 to 10%, relative to control), accompanied by a small reduction in food intake. The control group also showed reduced body weight gain from SD 1 to SD 8. At the end of recovery, average body weight of the high dose (HD) group was slightly reduced (5% in males and 7% in females), relative to control.**

Clinical chemistry parameters showed increased liver enzymes (AST, ALT, LDH**, and GLDH), but no microscopic findings in liver were observed. The expected reduction in plasma IgG was observed, which was dose-related in magnitude (up to 57% in the HD group).**

Because the bodyweight changes were slight and the liver enzyme elevations **were not associated with microscopic findings, the no-adverse-effect-level (NOAEL) was determined to be the HD of 100 mg/kg ($AUC_{0-\infty}$ = 43526 µg*h/mL).**

Study Number: 33981

Title: 4-week **Subchronic Toxicity Study of ARGX-113 by Repeated Intravenous Administration to CD®rat Multi-Site Study**

Sprague-Dawley rats received injections of efgartigimod by IV infusion at dose levels of 0, 10, 30, or 100 mg/kg every other day for 28 days. An additional 28 dosing-free days were designated for recovery animals. Hematology parameters showed dose-related increases in absolute and relative eosinophil counts on SD 58. Clinical chemistry results showed non-dose-related

reductions in globulin levels. Small increases were observed in albumin (24-30%) and fibrinogen (~39% for males and ~15% for females on SD 58) levels were observed at all doses, but neither effect was dose-related. No test article-related effect on coagulation was observed.

The expected reduction in circulating IgG was observed (up to 80-85%, not dose-related); levels were within normal limits at the end of the recovery period. Dosing with efgartigimod did not affect levels of IgA or IgM. Some animals tested positive for ADAs during the dosing period, but the presence of ADAs did not have an effect on drug levels since the AUC at the end of the dosing period increased dose proportionally. During the recovery period, a larger percentage of animals from each group tested positive for ADAs; therefore, the presence of the test article in circulation may have had a masking effect on ADA measurement.

No significant macroscopic findings were observed at necropsy, but differences in organ weights were observed. Lymph node weights were elevated relative to body weight (up to 25%) in males. In females, kidney and liver weights were slightly elevated relative to body weight at the end of dosing. An adequate battery of tissues was evaluated microscopically. HD males and females showed hypertrophy and hyperplasia of Kupffer cells. Inflammatory responses were observed at the injection sites.

The NOAEL was determined to be the MD of 30 mg/kg, every other day ($AUC_{0\text{-}672\ hr}$ = 200293 µg*h/mL for males and 221362 µg*h/mL for females).

Study Number/ Title: 31554

Title: 4-week Subchronic Toxicity Study of ARGX-113 by Repeated 2-hour Infusion to Cynomolgus Monkeys

Cynomolgus monkeys received efgartigimod via a 2-hour IV infusion at dose levels of 0, 3, 30, or 100 mg/kg every 48 hours for 28 days, followed by a 28-day recovery period. The target organ was liver. Increased ALT was observed at the end of the dosing period in HD males and females. Hematology results showed dose-related increases in large unnucleated cells in all dose groups. No other in-life changes were observed.

The expected reduction in IgG in all dose groups was up to 50-68%. The magnitude of the effect decreased with continued dosing, most likely due to ADA development. However, at the end of the dosing period, the AUC for each dose group was dose proportional.

Liver weights were slightly elevated relative to body weight (10% at the MD and HD) at the end of the dosing period. Microscopic findings in the liver (hepatocyte degeneration and diffuse mixed inflammatory cells with dilation of sinusoids) were observed at the HD in males and females.

Inflammatory effects were observed at the injection sites in all groups including controls but showed a dose-related exacerbation in severity.

The NOAEL was determined to be the MD (30 mg/kg every 48 hours) based on liver histopathology, correlated with clinical chemistry findings. Plasma exposures ($AUC_{(0\text{-}647h)}$) at the NOAEL were 200.020 ± 21.478 mg*h/mL in males and 180.370 ± 9.757 mg*h/mL in females.

Study Number/ Title: 33260

Title: 26-week **Chronic Toxicity Study of ARGX-113 by Repeated 30-minute Intravenous Infusion to Cynomolgus Monkeys with an 8-week Recovery Period**

Cynomolgus monkeys were dosed with **efgartigimod weekly by IV 30-minute infusion for 26 weeks at dose levels of 0, 10, 30, or 100 mg/kg. The product was well tolerated at all dose levels.**

Reductions in red cell mass (graded slight) were observed in HD animals on SD 93 and 184, relative to baseline. Eosinophils counts were elevated (up to 2.5X relative to control and baseline) in MDM and HDM. This finding was not observed in females.

Dose-related reductions in globulins accompanied by increases in A:G ratio were observed. These findings are expected due to the pharmacological activity of the test article.

Reductions of endogenous IgG were observed at all dose levels relative to control (peak of 50-54% after the first and second dose). The magnitude of reduction decreased with continued dosing, most likely due to ADA development. ADAs were detected in all dosed animals. The AUC for both males and females declined from SD 85 to SD 177, suggesting the development of neutralizing ADAs.

The NOAEL was determined to be the HD of 100 mg/kg/week ($AUC_{0-\infty}$ = 20687µg*h/mL for males and 18091µg*h/mL for females).

13.1.3.2. Genetic Toxicology

Genetic toxicology studies were not conducted for efgartigimod.

Carcinogenicity assays were not conducted with this product. A carcinogenicity assessment was submitted to IND 132953 and agreement was reached that standard carcinogenicity studies would not be required.

13.1.3.3. Reproductive Toxicology

A full battery of reproductive toxicology studies was conducted in Sprague-Dawley rats and New Zealand White rabbits. In all studies, efgartigimod was administered by IV injection at doses of 0, 30, or 100 mg/kg.

Study Number: 35984

Title: Examination of the Influence of Efgartigimod on the Fertility and Early Embryonic Development to Implantation of Rats Following Intravenous Administration to the Animals of the F_0 Generation.

Efgartigimod was administered daily to male rats (20/group) daily beginning 4 weeks prior to mating until the day before sacrifice on SD43 or 44 and to females (20/group) beginning 2 weeks prior to mating until GD7. A slight reduction in spermatid count in both dose groups was observed, but there was no effect number of motile sperm or on the male fertility index. In females, the cycle length was longer in HD females. There were, however, no effects on the number of females pregnant, females with live fetuses, or the number of resorptions.

The NOAEL was determined to be the HD of 100 mg/kg, associated with a plasma $AUC_{0-\infty}$ of 9630.4 h*µg/mL in dams.

Study # 35986

Title: Embryo-Fetal Development in Rats with Efgartigimod by Intravenous Administration

Pregnant Sprague-Dawley rats (25/group) were administered ARGX-113 daily from GD 6 to GD 17. No effects on embryofetal development were observed. A slight dose-related increase in pre-implantation loss was noted.

The NOAEL was the HD of 100 mg/kg/day, associated with a plasma $AUC_{0-\infty}$ in dams of 6476.228 h*µg/mL on GD17.

Study # 35988

Title: Study of embryofetal development in rabbits with efgartigimod by intravenous administration

Pregnant New Zealand White rabbits (20/group) received IV doses of 0, 30 or 100 mg/kg daily from GD 6 to GD 28. Two LD females (GD28; 9.1% incidence) and one HD female (GD20;4.8% incidence) aborted. This rate was slightly greater than the conducting laboratory's historical spontaneous abortion rate (4.26% ± 4.18 with a range of 0.0 to 9.5%). There were no significant effects on Cesarean parameters or on embryofetal development. Cerebral hemorrhage was observed in 3 HD pups in different litters (15% litter incidence). The total fetal incidence was within the historical control range; however, litter incidence for historical controls was not provided.

The NOAEL for adverse effects on embryofetal development was the HD of 100 mg/kg/day due to the cerebral hemorrhage observed in fetuses at the HD. At the NOAEL, the plasma $AUC_{0-\infty}$ in dams was 26311.0 h*µg/mL on GD28.

Study #35989

Title: Examination of Efgartigimod for Effects on the Pre- and Postnatal Development (including Maternal Function) following Intravenous Administration to the Dams of Rats of the F_0 Generation

Pregnant Sprague-Dawley rats (25/group) received efgartigimod daily from GD 6 to lactation day (LD). One HD female died prematurely (GD 21). This death was considered due to "incipient abortion." A small, dose-related increase in non-pregnant females was observed. No test article-related effects were observed on gestation length, gestation index, or preweaning litter parameters (including implantation, liveborn pups, postnatal survival). There were also no drug-related effects on postnatal developmental landmarks or neurobehavioral function. However, the learning and memory evaluation did not include a complex maze as is usually expected. There were no significant effects on mating parameters in offspring or on F_2 fetal development. There was a slight reduction in the number of pregnant F_1 females, but the effect was not dose-related in magnitude.

The NOAEL was determined to be the HD of 100 mg/kg, which was associated with a plasma $AUC_{0-\infty}$ in dams of 74720.7 h*µg/mL on GD28. No TK values were provided for the F_1 pups.

13.2. Individual Reviews of Studies Submitted to the New Drug Application

All nonclinical studies were reviewed under the IND.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Efgartigimod is a human IgG1 Fc-fragment modified to target and bind to FcRn receptor. It is neither subject to CYP450 metabolism nor expected to interfere with cytokine levels. Further, efgartigimod is not expected to be affected by transporters. Therefore, no in vitro transporter or CYP450-mediated drug interaction studies were conducted.

14.2. In Vivo Studies

14.2.1. Study ARGX-113-1501: Phase 1, Single- and Multiple-Ascending Dose Study

Study Design

The single ascending dose (SAD) part was conducted in five sequential (dose level) cohorts: 0.2, 2, 10, 25, and 50 mg/kg of 6 healthy subjects each (Cohorts 1 to 5), in which subjects were randomized to receive efgartigimod or placebo in a 4:2 ratio. A staggered approach was employed within all dose levels, and an interval of at least 14 days between dosing of the first subject in the first SAD dose level and dosing of first subject in each subsequent SAD dose level, was observed. Blood samples were collected predose, and 2, 4, 8, 24, 48, 72, 96, 144, 336, 504, and 672 hours postdose, and urine samples were collected between the first void (at which the subjects emptied their urinary bladder) until 0 hours predose and according to the following windows postdose: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 48 hours, and 48 to 72 hours.

The multiple ascending dose (MAD) part was conducted in 4 cohorts (Cohorts 7 to 10) of 8 healthy subjects each—10 mg every 4 days for 6 infusions, 25 mg/kg every 7 days (q7d) for 4 infusions, 10 mg/kg q7d for 4 infusions, and 25 mg/kg q7d for 4 infusions —in which subjects were randomized to receive efgartigimod or placebo in a 6:2 ratio. Dosing in Cohort 8 was discontinued for precautionary reasons because one subject experienced a serious adverse event (SAE) even though the study investigator considered the SAE unlikely to be related to study drug. Per protocol amendment 4, dosing in Cohort 10 was conducted at the same dosing regimen as in Cohort 8. A staggered approach was employed within all dose levels, and an interval of at least 14 days between dosing of the first subject in the first MAD dose level and dosing of the first subject in each subsequent MAD dose level was observed. Blood samples were collected predose, and 2, 8, 24, 72, and 120 hours postdose relative to the Day 1, 8, and 15 administrations, and predose, and 2, 8, 24, 48, 72, 120, 144, 216, 336, 504, 672, 1008, and 1344 hours postdose relative to the Day 22 administration.

Results

The results from SAD and MAD part are summarized in Table 57 and Table 58 below:

Table 57. Summary of Efgartigimod Pharmacokinetic Parameters and Dose Proportionality of PK Parameters, Single-Ascending Dose Part, Study 1501

	Part 1: Single Ascending Dose					
PK Parameter	0.2 mg/kg N=4	2.0 mg/kg N=4	10 mg/kg N=4	25 mg/kg N=4	50 mg/kg N=4	Slope: PE and 90% CI[a]
Cmax (µg/mL)	1.81 (15.8)	34.8 (14.8)	209 (13.4)	436 (10.9)	1175 (42.0)	1.1306 (1.0824-1.1788)
t_{max} (h)	2.0 (2.0-2.1)	2.0 (2.0-2.0)	2.1 (2.0-2.3)	2.0 (2.0-2.0)	2.0 (2.0-4.0)	-
C_{96h} (µg/mL)	0.157 (115)	2.02 (10.0)	19.2 (28.8)	27.9 (23.2)	45.6 (23.4)	-
AUC_{0-t} (µg.h/mL)	103 (123)	936 (5.76)	6770 (22.5)	12763 (16.4)	23340 (12.9)	-
AUC_{0-96h} (µg.h/mL)	41.9 (39.3)	694 (4.74)	4616 (15.1)	8584 (12.9)	17423 (16.2)	-
AUC_{inf} (µg.h/mL)	$NC^{n=0}$	998 (5.89)	6818 (22.3)	12826 (16.4)	23435 (13.0)	0.9522 (0.8866-1.0178)
$t_{1/2,\lambda z}$ (h)	140 (78.2)$^{n=3}$	104 (7.55)	85.1 (8.81)	89.7 (2.60)	91.3 (5.31)	-
CL (L/h)	$NC^{n=0}$	0.142 (13.8)	0.122 (22.0)	0.153 (13.7)	0.163 (14.8)	-
V_z (L)	$NC^{n=0}$	21.4 (15.6)	14.8 (13.7)	19.8 (11.5)	21.4 (10.7)	-
Ae_{0-72h} (%dose)	0.00 (NC)	0.00 (NC)	0.0124 (81.5)	0.0238 (58.7)	0.0845 (21.1)$^{n=3}$	-
CL_R (L/h)	0.00 (NC)	0.00 (NC)	0.0000226 (75.1)	0.0000582 (59.4)	0.000206 (15.4)$^{n=3}$	-

N=number of subjects; NC=not calculated, n=number of subjects with data
Values are arithmetic means (CV%) except median (min-max) for t_{max}
[a] Point estimate (PE) of the slope with 90% confidence interval (CI), from the power model on ln-transformed C_{max} and AUC_{inf} (dependent variable) and dose as fixed effect

Source: Study 1501: Table-10, Page 89
Abbreviations: Ae_{0-72h}, amount of dose excreted in the urine; AUC, area under the concentration-time curve; CI, confidence interval; CL, systemic clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects in treatment group; PK, pharmacokinetics; t_{max}, time to peak plasma concentrations; $t_{1/2}$, terminal half-life; V_z, volume of distribution

Table 58. Summary of Efgartigimod Pharmacokinetic Parameters, Multiple-Ascending Dose Part, Study 1501

	Part 2: Multiple Ascending Dose							
	10 mg/kg q7d N=6				25 mg/kg q7d[a] N=6			
PK parameter	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22
C_{max} (µg/mL)	195 (15.8)	202 (22.9)	237 (17.1)	204 (10.9)	535 (25.4)	393 (28.1)	407 (17.9)	485 (28.1)
t_{max} (h)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.1 (2.0-8.0)	2.0 (2.0-2.0)	2.0 (2.0-2.1)
C_{168h} (µg/mL)	8.02 (14.1)	10.2 (26.2)	10.2 (21.1)	NA	16.1 (33.3)	17.5 (20.9)	18.9 (24.1)	NA
AUC_{0-168h} (µg.h/mL)	5392 (11.5)	5936 (10.9)	6024 (9.01)	5612 (11.5)	12458 (25.0)	10315 (27.3)	10061 (19.6)	11152 (16.8)
R_{ac}	NA	1.10 (8.48)	1.12 (13.6)	1.04 (4.74)	NA	0.822 (12.4)	0.814 (14.5)	0.907 (12.9)

N=number of subjects, NA=not applicable; Values are arithmetic mean (CV%) except median (min-max) for t_{max} and geometric means (CV%) for R_{ac}
[a] For the q7d regimen at the dose 25 mg/kg, only the data from the Cohort 10 are summarized in this table.

Source: Study 1501: Table-12, Page 93
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects in treatment group; NA, not applicable; PK, pharmacokinetics; q7d, every 7 days; R_{ac}, accumulation ratio; t_{max}, time to peak plasma concentrations

Key Conclusions

- SAD part: Exposures, maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC_{inf}) increased in an approximately dose proportional manner between 2 mg/kg and 50 mg/kg. Median C_{max} occurred at 2 hours, i.e., the end of infusion. Efgartigimod was not quantifiable over a 0 to 72-

hour period following 0.2 and 2 mg/kg dosing but was quantifiable at higher dose levels. The excretion of efgartigimod in urine was very low (<0.1%).

- MAD part: Efgartigimod pharmacokinetics (PK) increased in a slightly less than dose-proportional manner following multiple dosing. The geometric mean accumulation ratios (R_{ac}) following q7d dosing suggested minimal accumulation, mean R_{ac} values ~1.0

Reviewer's comment*: The reviewer agrees with the Applicant's assessment. The reviewer verified the Applicant's bioanalytical method validation and performance and considers it acceptable for quantification of serum and urine efgartigimod concentrations in this study.*

14.3. Bioanalytical Method Validation and Performance

Efgartigimod exposures in serum and urine (as applicable in relevant study) were determined using a quantitative enzyme-linked immunosorbent assay (ELISA). Specifically, serum samples from Studies ARGX-113-1501 (Study 1501) and ARGX-1602 (Study 1602) and urine samples from Study 1501 were analyzed by an analytical method developed by the Applicant and then transferred to and validated at (b) (4) (reported in Module 5.3.1.4 – CP155054 for serum, and in Module 5.3.1.4 – CP155240 for urine). The method validation parameters and performance characteristics are summarized as Method #1 in tables below (Table 59 and Table 60).

Subsequently, a full revalidation of the method using a new reference batch was performed at (b) (4) (reported in Module 5.3.1.4 – CP180065) and this method was used for the pivotal phase 3 Study ARGX-113-1704 (Study 1704). The method validation parameters and performance characteristics are summarized as Method #2 in tables below (Table 61, and Table 62).

Table 59. Method Performance for Determination of Efgartigimod in Serum, Validation Method #1

Validation parameters	Method Validation Summary		Source Location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7 calibrators	CP155054, Table 15.2
	Inter assay accuracy (%bias) from LLOQ to ULOQ. Data presented is from all validation runs.	-2.80% to 4.00%	CP155054, Table 15.2
	Cumulative precision (%CV) from LLOQ to ULOQ. Data presented is from all validation runs.	≤5.82%	CP155054, Table 15.2
Performance of QCs during accuracy and precision runs	**Intra assay accuracy (%bias) in 5 QCs**	LLOQ 7.67% to 17.67% Low -4.83% to 4.00% Mid -8.67% to 0.67% High -11.25% to 10.00% ULOQ -7.00% to 12.00%	CP155054, Table 15.3
	Inter batch precision %CV	LLOQ ≤8.06% Low ≤6.33% Mid ≤7.11% High ≤14.22% ULOQ ≤16.10%	CP155054, Table 15.3
	Total error (TE)	LLOQ ≤21.39% Low ≤7.33% Mid ≤12.45% High ≤15.97% ULOQ ≤16.70%	CP155054, Table 15.3
Bench-top/process stability	Bench stability and refrigerator stability was investigated by storing initially frozen (-24°C±6°C and -75°C±10°C) stability samples for 17 hours and 10 minutes (after storage at -24°C±6°C) and for 17 hours and 30 minutes (after storage at -75°C±10°C) at room and refrigerator (+5°C±5°C) temperature. All stability results were within the acceptance criteria.		CP155054, Table 15.20 to Table 15.22
Freeze-Thaw stability	Freeze-thaw stability was investigated by submitting stability samples stored at -24°C±6°C and -75°C±10°C to 3 freeze-thaw cycles. All stability results were within the acceptance criteria.		CP155054, Table 15.19
Long-term storage	Long term stability was investigated by storing stability samples stored at -24°C±6°C and -75°C±10°C for 378 days. Based on the results, efgartigimod in serum is considered stable at tested temperatures for up to 378 days.		CP155054, Table 15.23 and Table 15.24
Robustness	Coated plates were determined stable for 10 days at +5°C±5°C. Inter-analyst precision was ≤8.45%.		CP155054, Table 15.17 and Table 15.15

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 3
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Table 60. Method Performance for Determination of Efgartigimod in Serum, Validation Method #1, Studies 1501 and 1602

Method Performance in Study ARGX-113-1501 (Part 1) (Module 5.3.1.4, CP155247)		
Assay passing rate	13 of the 21 analytical runs passed (62% passing rate).	CP155247, Table 20.1
Standard curve performance	Inter assay bias range: -2.33% to 5.00% Inter assay precision: ≤6.74% CV Results presented are of accepted runs.	CP155247, Table 20.2
QC performance	Inter assay bias range: -10.00% to -6.50% Inter assay precision: ≤12.76% CV	CP155247, Table 20.4
Method reproducibility	Incurred sample re-analysis was not performed in this study.	*NA*
Study sample analysis/ stability	Stability of efgartigimod in human serum at -75°C±10°C was demonstrated for up to 378 days (CP155054). First sample was collected on 19-Oct-2015 and last sample was analyzed on 08-Apr-2016 (ie, 172 days).	CP155247, Section 9.5
Standard calibration curve performance during accuracy and precision runs	Calibration curve contains 7 standards from LLOQ to ULOQ.	
Method Performance in Study ARGX-113-1501 (Part 2) (Module 5.3.1.4, CP155248)		
Assay passing rate	33 of the 49 analytical runs passed (67% passing rate).	CP155248, Table 19.1
Standard curve performance	Inter assay bias range: -3.20% to 7.00% Inter assay precision: ≤7.59% CV Results presented are of accepted runs.	CP155248, Table 19.2
QC performance	Inter assay bias range : -10.75% to -5.83% Inter assay precision: ≤15.07% CV	CP155248, Table 19.4
Method reproducibility	Incurred sample re-analysis was not performed in this study.	*NA*
Study sample analysis/ stability	Stability of efgartigimod in human serum at -75°C±10°C was demonstrated for up to 378 days (CP155054). First sample was collected on 27-Jan-2016 and last sample was analyzed on 31-Oct-2016 (ie, 278 days).	CP155248, Section 9.5
Standard calibration curve performance during accuracy and precision runs	Calibration curve contains 7 standards from LLOQ to ULOQ.	
Method Performance in Study ARGX-113-1602 (Module 5.3.1.4, CP165307)		
Assay passing rate	7 of the 10 analytical runs passed (70.0% passing rate).	CP165307, Table 19.1
Standard curve performance	Inter assay bias range: -2.50% to 4.80% Inter assay precision: ≤6.63% CV Results presented are of accepted runs.	CP165307, Table 19.2
QC performance	Inter assay bias range: -11.00% to -8.67% Inter assay precision: ≤16.04% CV	CP165307, Table 19.3
Method reproducibility	Incurred sample re-analysis was not performed in this study.	*NA*
Study sample analysis/ stability	Stability of efgartigimod in human serum at -75°C±10°C was demonstrated for up to 378 days (CP155054). First sample was collected on 25-Jan-2017 and last sample was analyzed on 09-Nov-2017 (ie, 288 days).	CP165307, Section 9.5

Source: Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 3
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; NA, not applicable; QC, quality control; ULOQ, upper limit of quantitation

Table 61. Method Performance for Determination of Efgartigimod in Serum, Validation Method #2

Validation parameters	Method Validation Summary		Source Location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ.	7 calibrators	CP185065, Table 20.7
	Inter assay accuracy (%bias) from LLOQ to ULOQ. Data presented is from all validation runs.	-2.56% to 7.00%	CP185065, Table 20.7
	Cumulative precision (%CV) from LLOQ to ULOQ. Data presented is from all validation runs.	≤10.02%	CP185065, Table 20.7
Performance of QCs during accuracy and precision runs	**Intra run accuracy (%bias) in 5 QCs**	LLOQ -22.00% to 12.00% Low -16.67% to 11.50% Mid -14.00% to 14.67% High -14.67% to 18.00% ULOQ -18.50% to 17.25%	CP185065, Table 20.9
	Inter batch precision %CV	LLOQ ≤16.86% Low ≤13.71% Mid ≤14.42% High ≤14.27% ULOQ ≤15.41%	CP185065, Table 20.9
	Total error (TE)	LLOQ ≤21.20% Low ≤14.88% Mid ≤16.42% High ≤16.60% ULOQ ≤21.16%	CP185065, Table 20.9
Bench-top/process stability	Bench-top and refrigerator stability was investigated by storing initially frozen (-24°C±6°C and -75°C±10°C) stability samples for 18 hours at room temperature or in the refrigerator (+5°C±5°C). All stability results were within the preset acceptance criteria.		CP185065, Table 20.18
Freeze-Thaw stability	Freeze-thaw stability was investigated by submitting stability samples stored at (-24°C±6°C and -75°C±10°C to 5 freeze-thaw cycles. All stability results were within the preset acceptance criteria.		CP185065, Table 20.17
Long-term storage	Long term stability was investigated by storing stability samples at -24°C±6°C and -75°C±10°C for 182 days. Based on the results, efgartigimod in serum is considered stable for up to 182 days.		CP185065, Table 20.19 and Table 20.20
Robustness	Coated plates were determined stable for 6 days at +5°C±5°C. Coating antibody was retested and expiry data was extended till 19-Apr-2019. Inter-analyst precision was <7% at the LLOQ and ULOQ level and within ±6% at the other QC levels.		CP185065, Table 20.10, Table 20.14, and Table 20.21

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 4
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Table 62. Method Performance for Determination of Efgartigimod in Serum, Validation Method #2, Study 1704

Method Performance in Study ARGX-113-1704 (Module 5.3.1.4, CP185211)		
Assay passing rate	85 of the 113 analytical runs passed (75% passing rate)	CP185211, Table 23.1
Standard curve performance	Inter assay bias range: -3.70% to 8.75% Inter assay precision: ≤8.14% CV Results presented are of accepted runs.	CP185211, Table 23.10
QC performance	Inter assay bias range: 1.50% to 8.00% Inter assay precision: ≤12.38% CV	CP185211, Table 23.11
Method reproducibility	Incurred sample re-analysis was performed in 10.0% of study samples, and 70.00% of the samples met the pre-specified criteria.	CP185211, Table 23.12
Cross validation of efgartigimod batches	A new reference substance (Batch/Lot No. P63505A) was cross validated and successfully compared with the old reference substance (Batch/Lot No. P63504A).	CP185211, Table 23.8 and Table 23.9
Qualification runs	Qualification of new HRP batch, Batch/Lot No. GR2158800-3 (new batch) was qualified compared to GR3305908-2 (old batch) and accepted for further use. Qualification of a technician.	CP185211, Table 23.2 to Table 23.7
Study sample analysis/ stability	Stability of efgartigimod in human serum at -75°C±10°C was demonstrated for up to 548 days (CP185065). This stability period covers the maximum length of time from specimen collection to analysis i.e., 412 days.	CP185211, Section 9
Standard calibration curve performance during accuracy and precision runs	Calibration curve contains 7 standards from LLOQ to ULOQ	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 4
Abbreviations: CV, coefficient of variation; HRP, horseradish peroxidase; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Reviewer's comment: *The reviewer agrees that the bioanalytical method validation and performance is adequate for quantification of serum efgartigimod concentrations in Studies 1501, 1602, and 1704 and are in accordance with the criteria for accuracy and precision (including incurred sample reanalysis for Study 1704) outlined in the FDA bioanalytical guidance. The reviewer notes that though the "passing rate" indicated in the tables above are in the 62 to 75% range primarily due to technical reasons and QC failing to meet the criteria, all the "failed" runs passed the criteria in subsequent runs. Overall, the serum efgartigimod concentrations measured in these studies are reliable.*

Table 63. Method Performance for Determination of Efgartigimod in Urine

Validation parameters	Method Validation Summary		Source Location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ.	7 calibrators	CP155240, Table 15.2
	Intra assay accuracy (%bias) from LLOQ to ULOQ. Data presented is from all validation runs.	-4.10% to 11.13	CP155240, Table 15.2
	Cumulative precision (%CV) from LLOQ to ULOQ. Data presented is from all validation runs.	≤7.03%	CP155240, Table 15.2
Performance of QCs during accuracy and precision runs	**Intra assay accuracy (%bias) in 5 QCs**	LLOQ -1.20% to 5.60% Low -4.00% to 6.00% Mid -11.00% to -5.00% High -14.88% to -4.78% ULOQ -18.50% to -4.80%	CP155240, Table 15.3
	Inter batch %CV	LLOQ ≤5.13% Low ≤5.43% Mid ≤5.98% High ≤11.96% ULOQ ≤11.12%	CP155240, Table 15.3
	Total error (TE)	LLOQ ≤7.33% Low ≤6.43% Mid ≤13.98% High ≤20.09% ULOQ ≤24.72%	CP155240, Table 15.3
Bench-top/process stability	Bench top stability and refrigerator stability was investigated by storing initially frozen (-24°C±6°C and -75°C±10°C) stability samples for 18 hours and 30 minutes at room and refrigerator temperature. All stability results were within the preset acceptance criteria.		CP155240, Table 15.12 and Table 15.13
Freeze-Thaw stability	Freeze-thaw stability was investigated by submitting stability samples stored at -24°C±6°C and -75°C±10°C concentration to 3 freeze-thaw cycles. All stability results were within the preset acceptance criteria.		CP155240, Table 15.11
Long-term storage	Long term stability was investigated by storing stability samples stored at -24°C±6°C and -75°C±10°C for 382 days. Based on the results, efgartigimod in urine is considered stable at tested temperatures for up to 382 days.		CP155240, Table 15.14 and Table 15.15

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 5
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Table 64. Method Performance for Determination of Efgartigimod in Urine, Study 1501

Method Performance in Study ARGX-113-1501 (Part 1) (Module 5.3.1.4, CP155247)		
Assay passing rate	7 of the 7 analytical runs passed (100% passing rate).	CP155247, Table 20.1
Standard curve performance	Inter assay bias range: -2.70% to 6.50% Inter assay precision: ≤9.23% CV	CP155247, Table 20.5
QC performance	Inter assay bias range: -6.00% to 2.00% Inter assay precision: ≤13.77% CV	CP155247, Table 20.7
Method reproducibility	Incurred sample re-analysis was not performed in this study.	*NA*
Study sample analysis/ stability	Stability of efgartigimod in human urine at -75°C±10°C was demonstrated for up to 382 days (CP155240). First sample was collected on 19-Oct-2015 and last sample was analyzed on 04-Jan-2016 (ie, 77 days).	CP155247, Section 9.5
Standard calibration curve performance during accuracy and precision runs	Calibration curve contains 7 standards from LLOQ to ULOQ.	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1) Table 4
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; NA, not applicable; QC, quality control; ULOQ, upper limit of quantitation

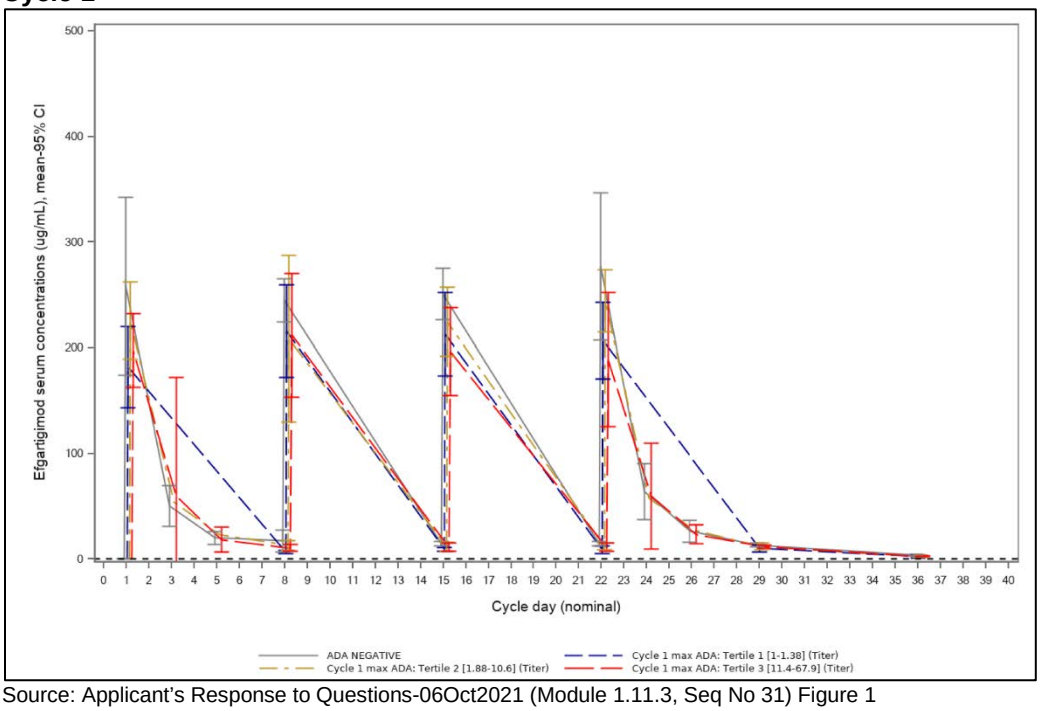
Reviewer's comment: *The reviewer agrees that the bioanalytical method validation and performance is adequate for quantification of urine efgartigimod concentrations in Study 1501 and are in accordance with the criteria for accuracy and precision outlined in the FDA bioanalytical guidance.*

14.4. Immunogenicity Assessment – Impact on PK/PD, Efficacy and Safety

The antidrug antibody (ADA) assessments were conducted by Office of Biotechnology Products (OBP) review team and summarized in their review. OBP review team noted bioanalytical assay concerns with quantification of neutralizing antibodies; therefore, the assessment of incidence of only the total ADA on the clinical impact was conducted (summarized below).

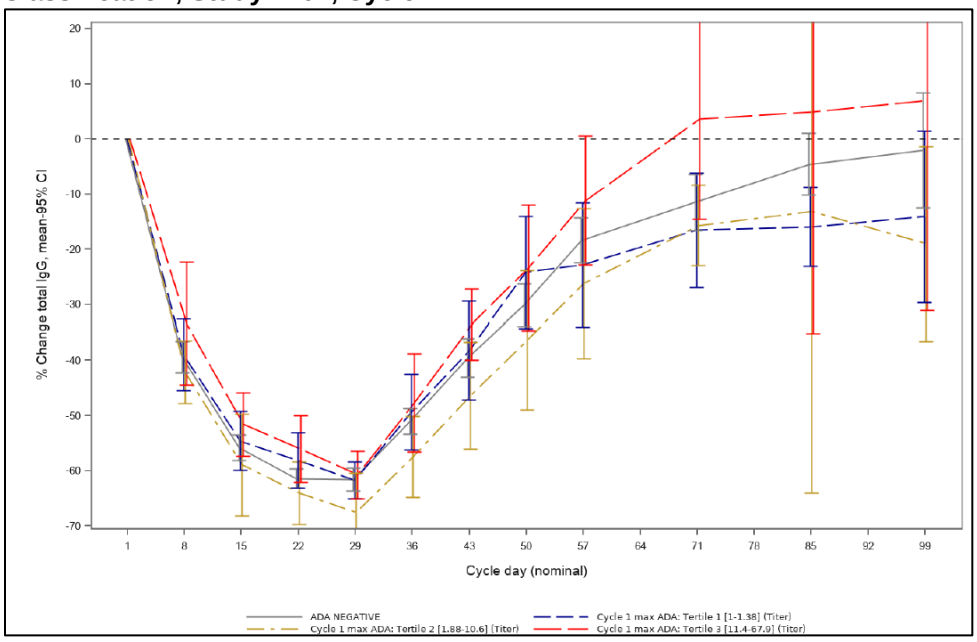
The response (received on October 12, 2021) to an information request (sent on October 6, 2021) on correlation analysis at group-level across subject groups with different titer levels across cycles in Study 1704 is summarized below. Briefly, the subjects were divided into 3 groups based on ADA titer per tertiles according to the highest titer observed within the cycle. The impact of ADA per titer group on PK, pharmacodynamic (PD; total IgG reduction), and efficacy measures (Myasthenia Gravis-Specific Activities of Daily Living [MG-ADL] and Quantitative Myasthenia Gravis [QMG] scores) was determined. Overall, as summarized in the figures below (Figure 7, Figure 8, Figure 9, and Figure 10), there is no clear evidence of an impact of ADA on PK/PD and efficacy profiles of efgartigimod. However, the available data are too limited to make definitive conclusions.

Figure 7. Efgartigimod Serum Concentrations by ADA Titer Classification by Cycle, Study 1704, Cycle 1



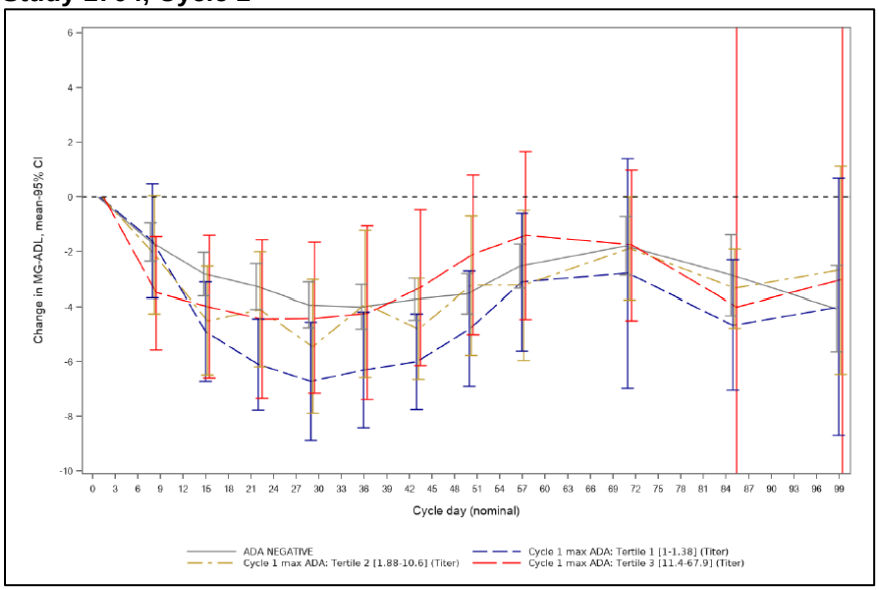
Source: Applicant's Response to Questions-06Oct2021 (Module 1.11.3, Seq No 31) Figure 1
Abbreviations: ADA, antidrug antibody CI, confidence interval

Figure 8. Mean Percent Change From Cycle Baseline in Total IgG Levels by ADA Titer Classification, Study 1704, Cycle 1



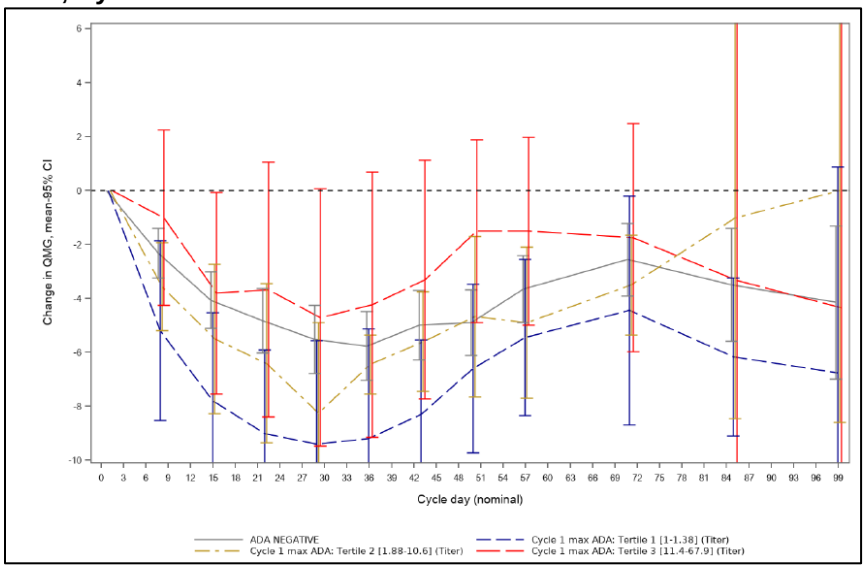
Source: Applicant's Response to Questions-06Oct2021 (Module 1.11.3, Seq No 31) Figure 5
Abbreviations: ADA, antidrug antibody; CI, confidence interval; IgG, immunoglobin G

Figure 9. Change From Cycle Baseline in MG-ADL Score by ADA Titer Classification by Cycle, Study 1704, Cycle 1



Source: Applicant's Response to Questions-06Oct2021 (Module 1.11.3, Seq No 31) Figure 9
Abbreviations: ADA, antidrug antibody; CI, confidence interval; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living

Figure 10. Change From Cycle Baseline in QMG Score by ADA Titer Classification by Cycle, Study 1704, Cycle 1



Source: Applicant's Response to Questions-06Oct2021 (Module 1.11.3, Seq No 31) Figure 13
Abbreviations: ADA, antidrug antibody; CI, confidence interval; QMG, Quantitative Myasthenia Gravis

14.5. Pharmacometrics Review

14.5.1. Applicant's Analysis

The PK/PD data were obtained from gMG subjects enrolled in one randomized, double-blind, placebo-controlled phase 2 study (Study 1602), one randomized, double-blind, placebo-controlled, multicenter phase 3 study (Study 1704), and its long-term open-label extension trial

(Study 1705). Data from two clinical studies were used in the population PK analysis and a brief description of these studies is given in Table 65.

Table 65. Summary of the Characteristics of the Studies Used for PopPK/PD Analyses

Study	ARGX-113-1602 (Phase 2)	ARGX-113-1704 (Phase 3)	ARGX-113-1705 (Phase 3)
Design	Double-blinded, placebo- controlled	Double-blinded, placebo-controlled	Open-label extension of ARGX-113-1704
Study population	Subjects with gMG (AChR-Ab seropositive) N=24 (23 completed, 12 PBO, 12 Trt)	Subjects with gMG (AChR-Ab seropositive or seronegative) N=167 (83 PBO, 84 Trt)	Subjects with gMG (AChR-Ab seropositive or seronegative) (N=135)
Dosage and administration	Efgartigimod IV 10 mg/kg or matched placebo IV infusions over 2 hours in one treatment cycle of 4 infusions at weekly intervals (q7d for 4 infusions)	Efgartigimod IV 10 mg/kg or matched placebo IV infusions over 1 hour in treatment cycles of 4 infusions at weekly intervals (q7d for 4 infusions) Retreatment/subsequent cycles of 4 infusions at weekly intervals initiated based on clinical response	Efgartigimod IV 10 mg/kg IV infusions over 1 hour in treatment cycles of 4 infusions at weekly intervals (q7d for 4 infusions) Retreatment/subsequent cycles of 4 infusions at weekly intervals initiated based on clinical response
PK assessments (serum)	At predose and within 30 min after the end of infusion on days 1, 8, 15 and 22 and up to 28 days after the 4th infusion	At predose and within 1 hour after the end of infusion on days 1, 8, 15 and 22 and up to 14 days after 4th infusion of each cycle and at EoS/ED	No PK samples taken
PD assessments (serum)	Total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM and AChR-Ab. At predose on days 1, 8, 15 and 22, and up to 56 days after the 4th infusion	Total IgG, IgG1, IgG2, IgG3, IgG4, AChR-Ab and anti- MuSK antibodies At predose on days 1, 8, 15 and 22 and up to 35 days after the 4th infusion of each cycle, every 2 weeks in the inter treatment cycle period, at each unscheduled visit and at EoS/ED	Total IgG, IgG1, IgG2, IgG3, IgG4, AChR-Ab and anti-MuSK antibodies, At predose on days 1, 8, 15 and 22 and up to 30 days after the 4th infusion of each cycle, every 30 days in the inter treatment cycle period, at each unscheduled visit and at the end-of-part A/ED

Source: Adapted from Summary of Clinical Pharmacology, Table 2 on Page 8-9.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; ED, early discontinuation; EoS, end of study; gMG, generalized myasthenia gravis; IgG, immunoglobin G; IV, intravenous; MuSK, muscle specific kinase; PBO, placebo; PD, pharmacodynamic; PK, pharmacokinetic; q7d, every 7 days; Trt, treatment

The final dataset for the population PK analysis consisted of a total of 1397 quantifiable efgartigimod serum concentrations from a total of 84 subjects. In total, 214 out of 1614 PK observations (13.3%) were below the lower limit of quantitation (LLOQ). Of these, 130 postdose PK observations were below the LLOQ (8%).

The final dataset for the efgartigimod PK/PD analysis includes PK, total IgG, and binding AChR-Ab observations for both Study 1704 and Study 1705. It consisted of a total of 4020 total IgG observations (3031 from Study 1704 [N=167], 989 from Study 1705 [N=125]), and 2283 AChR-Ab observations (N=129).

The structural population PK model consisted of a three-compartment model with linear clearance and included the assumption that the volume of the third (peripheral) compartment

(V3) was equal to the volume of the second (peripheral) compartment (V2). The inter-individual variability (IIV) was estimated for clearance (CL), V1, Q2, and the volume of the peripheral compartments (V2 = V3). Lastly, an additive error model was used to characterize the residual variability.

First, an exploratory covariate analysis was performed to investigate any potential relationships between the random-effect parameters and the categorical covariates or the continuous covariates. A formal covariate analysis was performed to investigate the influence of the preselected covariates (age, body weight, body mass index (BMI), race, ethnicity, gender, estimated glomerular filtration rate (eGFR), albumin, total bilirubin (BILI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ADA status, and gMG concomitant medication (i.e., nonsteroidal immunosuppressive drugs (NSIDs) only, steroids only, both NSIDs and steroids, or neither of both)) on CL and V1. Subsequently, a single addition, forward inclusion, and backwards elimination was conducted, and statistical significance of covariate-parameter relationship was evaluated based on likelihood ratio test. The final covariate model consisted of weight on V1 and CL and eGFR on CL. The Applicant generated forest plots to assess the impact of the covariate effects on exposure ($AUC_{0\text{-}168h}$ after the fourth weekly infusion).

PK/Total IgG Modeling

The existing PK/total IgG model for efgartigimod developed to describe total IgG data from MG subjects enrolled in the phase 2 Study 1602 was applied to total IgG data from Study 1704. IIV was identified for baseline IgG levels and for the potency (half maximal effective concentration) of efgartigimod using log-normal distribution; a proportional error model was used. To improve the description of the total IgG concentration across populations and cycles in the phase 3 study, the parameters were optimized on the Study 1704 data (model B.tIgG).

A slightly slower clearance (i.e., 12%) was shown in subjects with gMG based on the population PK model. Similarly, the population PK/PD model confirmed that the profile of IgG reduction (total IgG as well as the IgG1 subtype) was comparable in healthy subjects and subjects with gMG.

A statistically significant covariate effect of body weight on CL and V1 and of eGFR on CL was identified in the population PK model. The final parameter estimates are shown in Table 66. The population PK model was assessed with diagnostics plots including goodness-of-fit (Figure 11).

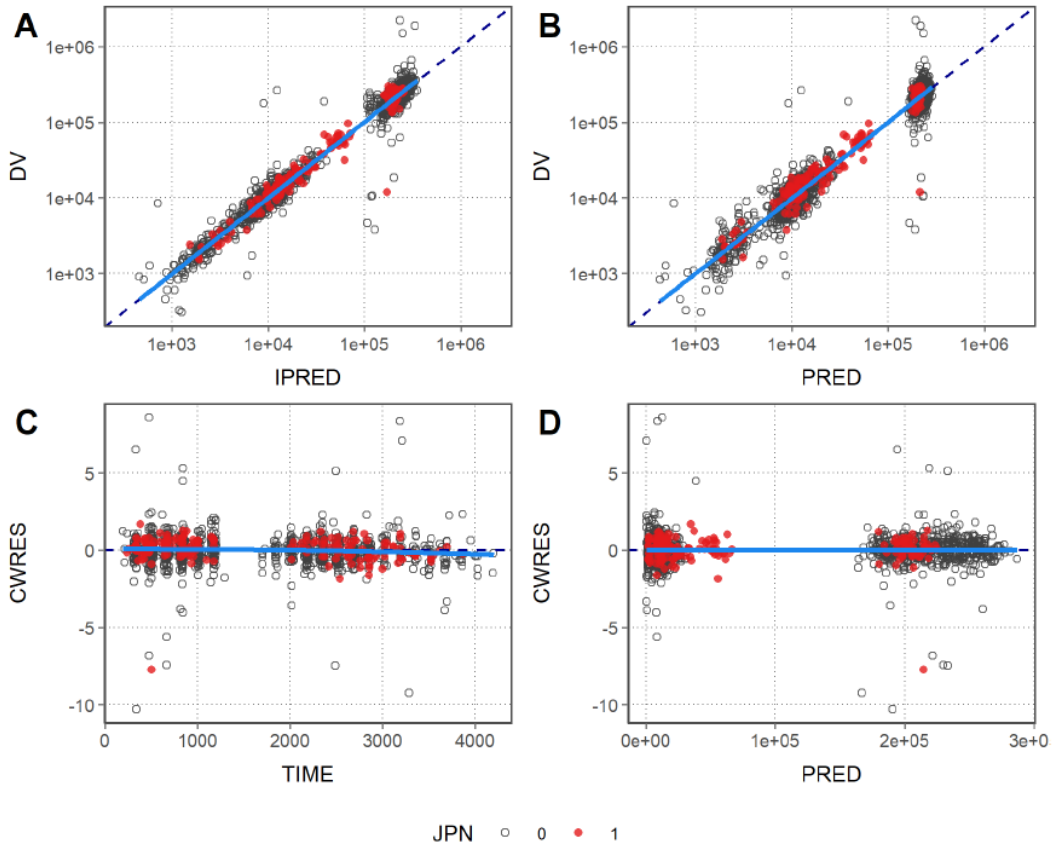
Table 66. Parameter Estimates of Applicant's Final Population PK Model (I.PK.mod)

Parameter Name	Estimate	SE	RSE (%)	95% CI
CL (L/h)	0.108	0.00270	2.50	(0.102 - 0.113)
V1 (L)	3.31	0.113	3.40	(3.09 - 3.53)
Q2 (L/h): FIXED	0.00511	-	-	-
V2 (L)	4.72	0.326	6.90	(4.09 - 5.36)
Q3 (L/h)	0.242	0.0506	20.9	(0.143 - 0.341)
weight on V1	0.590	0.0871	14.7	(0.420 - 0.761)
egfr on CL	0.453	0.0833	18.4	(0.290 - 0.617)
weight on CL	0.272	0.0469	17.2	(0.180 - 0.364)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
ω^2 CL	0.0177	0.00302	17.1	13.4
ω covariance CLxV1	0.0160	0.00594	37.2	51.2
ω^2 V1	0.0527	0.0151	28.7	23.3
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
Add error (in log)	0.127	0.0226	17.8	0.356

RSE (%) is calculated as SE/Estimate*100;4 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of an exponential error model, or sqrt(OM)/TH*100 in case of an additive error model; StDev is calculated as sqrt(SIG). The correlation coefficient for the covariance element (reported in the %CV column) is calculated as $100\% \cdot (\omega_{\text{covariance1x2}})/(\text{sqrt}(\exp(\omega_1^2) - 1) * \text{sqrt}(\exp(\omega_2^2) - 1))$.

Source: Applicant's popPK report efg 20-004 Page-80, Table 17
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; egfr, estimated glomerular filtration rate; PK, pharmacokinetic; RSE, relative standard error; SE, standard error; stDev, standard deviation

Figure 11. Goodness-of-Fit Plots for the Final PK Model I.PK.mod, All Cycles



Source: Applicant's popPK report efg 20-004 Page149, Figure 89
A: DV versus IPRED. B: DV versus PRED. C: CWRES versus time (in hours). D: CWRES versus PRED. Blue line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating 0 (C and D). Red dots: DV and CWRES values for observations from Japanese subjects. Black open circles: DV and CWRES values for observations from non-Japanese subjects. DV, PRED, and IPRED are plotted in ng/mL
Abbreviations: CWRES, conditional weighted residual; DV, observations; IPRED, individual predictions; PK, pharmacokinetic; PRED, population predictions

The model predicted $AUC_{0\text{-}168h}$ after the fourth weekly infusion was used to assess the impact of body weight on exposure on a body weight-based dose and fixed absolute dose regimen. The effect of body weight on exposure is summarized in Table 67.

The covariate assessment showed that CL appears to increase with weight. However, due to the body weight-based dosing, body weight affected not just CL and V1, but also the absolute dose administered, resulting in an increase of exposure with increasing body weight. An increase in $AUC_{0\text{-}168h}$ after the fourth weekly infusion with increase of body weight can be inferred from the simulation results, thus a weight-based dose cap >120 kg was proposed to prevent further increase in exposure in subjects >120 kg.

Table 67. Body Weight Effect on $AUC_{0\text{-}168h}$ After the Fourth Weekly Infusion

Body weight	Relative AUC_{0-168h} difference compared to a reference subject of median body weight and eGFR (76.05 kg and 100.27 mL/min/1.73m^2)
Body weight based dosing	
53 kg (5th percentile)	-20% (90%CI: -27%, -13%)
129.8 kg (95th percentile)	+44% (90%CI: +30%, +59%)
120 kg	+36% (90%CI: +24%, +49%)
Fixed absolute dose (760.5 mg based on the median body weight of 76.05 kg)	
53 kg (5th percentile)	+15% (90%CI: +5%, +25%)
129.8 kg (95th percentile)	-16% (90%CI: -24%, -7%)
120 kg	-14% (90%CI: -21%, -6%)

Source: Applicant's popPK report efg 20-004 Page 48, Table 8
Abbreviations: AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate

After four weekly infusions of efgartigimod 10 mg/kg, subjects with mild renal impairment (eGFR ≥60 mL/min/1.73m^2 but <90 mL/min/1.73m^2) showed a 28% (90% confidence interval [CI]: 19% to 37%) higher $AUC_{0\text{-}168h}$, compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2).

The final parameter estimates for total IgG are shown in Table 68.The final PK/PD model for efgartigimod was assessed with diagnostics plots including goodness-of-fit (Figure 12).

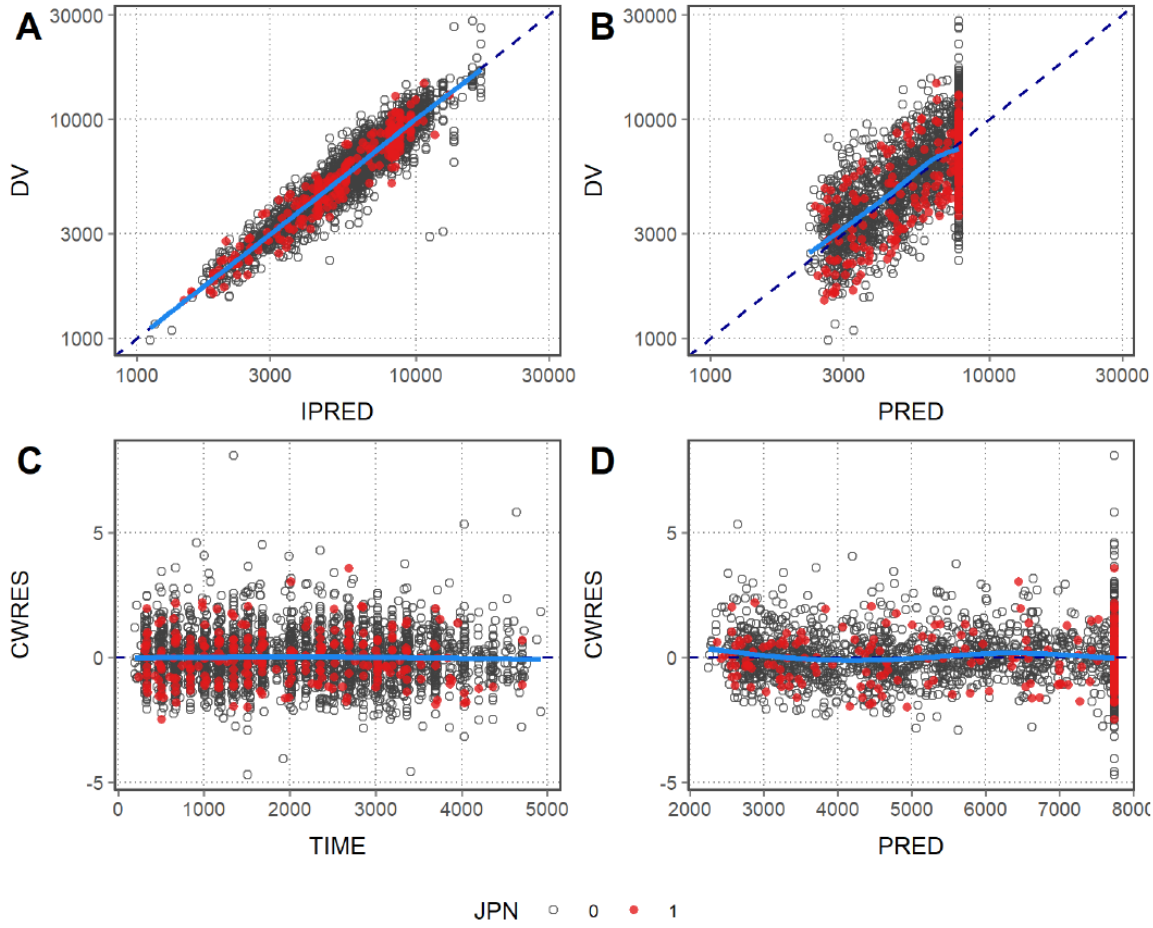
Table 68. Parameter Estimates of Final tIgG Model (E.tIgG.mod)

Parameter Name	Estimate	SE	RSE (%)	95% CI
BL-tIgG (μg/mL)	7744	166	2.14	(7419 - 8070)
Kout-tIgG (1/h)	0.00198	0.0000741	3.74	(0.00183 - 0.00212)
Emax-tIgG (-): FIXED	4.87	-	-	-
EC50-tIgG (ng/mL)	41407	2823	6.82	(35874 - 46940)
Hill-tIgG (-): FIXED	1.00	-	-	-
weight on EC50 (-)	0.741	0.179	24.1	(0.391 - 1.09)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
ω^2 BL-tIgG	0.0735	0.00863	11.7	27.6
ω^2 EC50-tIgG	0.192	0.0458	23.9	46.0
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
SIG Proportional Error tIgG	0.0214	0.00124	5.79	0.146

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of an exponential error model; StDev is calculated as sqrt(SIG)

Source: Applicant's popPK report efg 20-004 Page 84, Table 22
Abbreviations: CI, confidence interval; CV, coefficient of variation; EC50, half maximal effective concentration; Emax, maximal effective concentration; RSE, relative standard error; SE, standard error; stDev, standard deviation

Figure 12. Goodness-of-Fit Plots of Total IgG Obtained With the Final PK/Total IgG Model E.tIgG.mod, All Cycles



Source: Applicant's popPK report efg 20-004 Page200, Figure 147
A: DV versus IPRED. B: DV versus PRED. C: CWRES versus time (in hours). D: CWRES versus PRED. Blue line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating 0 (C and D). Red dots: DV and CWRES values for observations from Japanese subjects. Black open circles: DV and CWRES values for observations from non-Japanese subjects. DV, PRED, and IPRED are plotted in µg/mL.
Abbreviations: CWRES, conditional weighted residual; DV, observations; IgG, immunoglobin G; IPRED, individual predictions; PK, pharmacokinetic; PRED, population predictions

Reviewer's comment*: The reviewer agrees with the Applicant that the PK/PD profile of efgartigimod in gMG subjects can be adequately described by the proposed population PK/PD model. The reviewer was able to run the Applicant's final PK/PD model and obtained similar results as reported by the Applicant. Please see more details in Reviewer's Analysis below.*

14.5.2. Reviewer's Analysis

14.5.2.1. Objectives

- Evaluate the influence of age, body weight, renal function (mild and moderate renal impairment), hepatic impairment, sex, race, and body weight on the pharmacokinetics of efgartigimod.
- Evaluate the dosing regimen for missed/delayed dose scenarios

14.5.2.2. Methods

Datasets

Table 69. Datasets Used in Analyses

Study	Name	Link to EDR
Study 1704	NM.PKPD.ARG113.PH3.E.v10.xpt	\\CDSESUB1\evsprod\bla761195\0003\m5\datasets\20004\analysis\adam\datasets\definenm-pkpd-arg113-ph3-e-v10.pdf
Study 1704,1705	NM.PKPD.ARG113.PH3.E.v11.xpt	\\CDSESUB1\evsprod\bla761195\0003\m5\datasets\20004\analysis\adam\datasets\definenm-pkpd-arg113-ph3-e-v11.pdf
Study 1704	Adpc.xpt	\\CDSESUB1\evsprod\bla761195\0003\m5\datasets\argx-113-1704\analysis\adam\datasets\adpc.xpt

Source: Reviewer's analysis
Abbreviations: EDR, electronic document room

Software

Population PK model fitting was performed in NONMEM 7.4 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.2.

Models

The reviewers adopted the Applicant's final population PK and PK/PD model. The population PK model was a three-compartment model with linear clearance. The individual predicted PK parameters were used for PD simulation.

14.5.2.3. Results

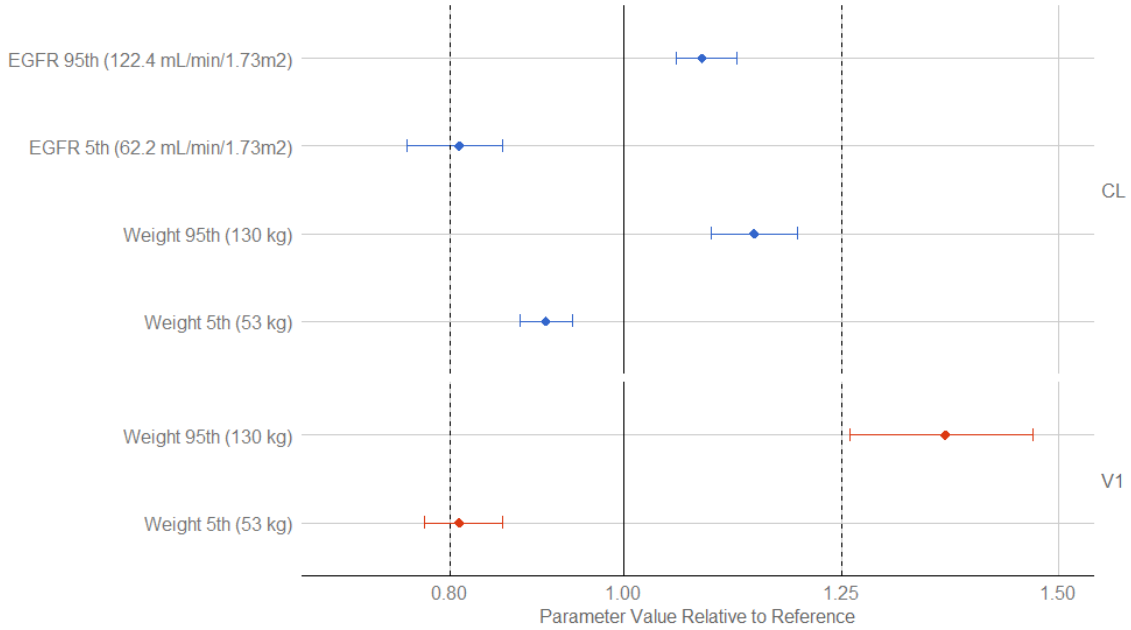
The reviewer was able to run the Applicant's final PK/PD model and obtained similar results as reported by the Applicant. In addition to the population PK model prediction, the review team considered the observed data along with the clinical pharmacology aspect of efgartigimod to make conclusions on the acceptability of proposed labeling statements.

Evaluation of Population PK and Population PK/PD Model

The reviewer was able to reproduce the model and obtain similar model diagnostics for population PK and population PK/PD models.

A forest plot (Figure 13) was constructed by bootstrapping to represent the estimated eGFR and weight effects in the model, showing the ratios comparing extreme values of covariate (5^{th} and 95^{th}) to median value and the associated 95% confidence intervals. Body weight was identified as a statistically significant covariate on volume of distribution. No significant covariate effect after weight and eGFR were included in the final model (Figure 14 and Figure 15).

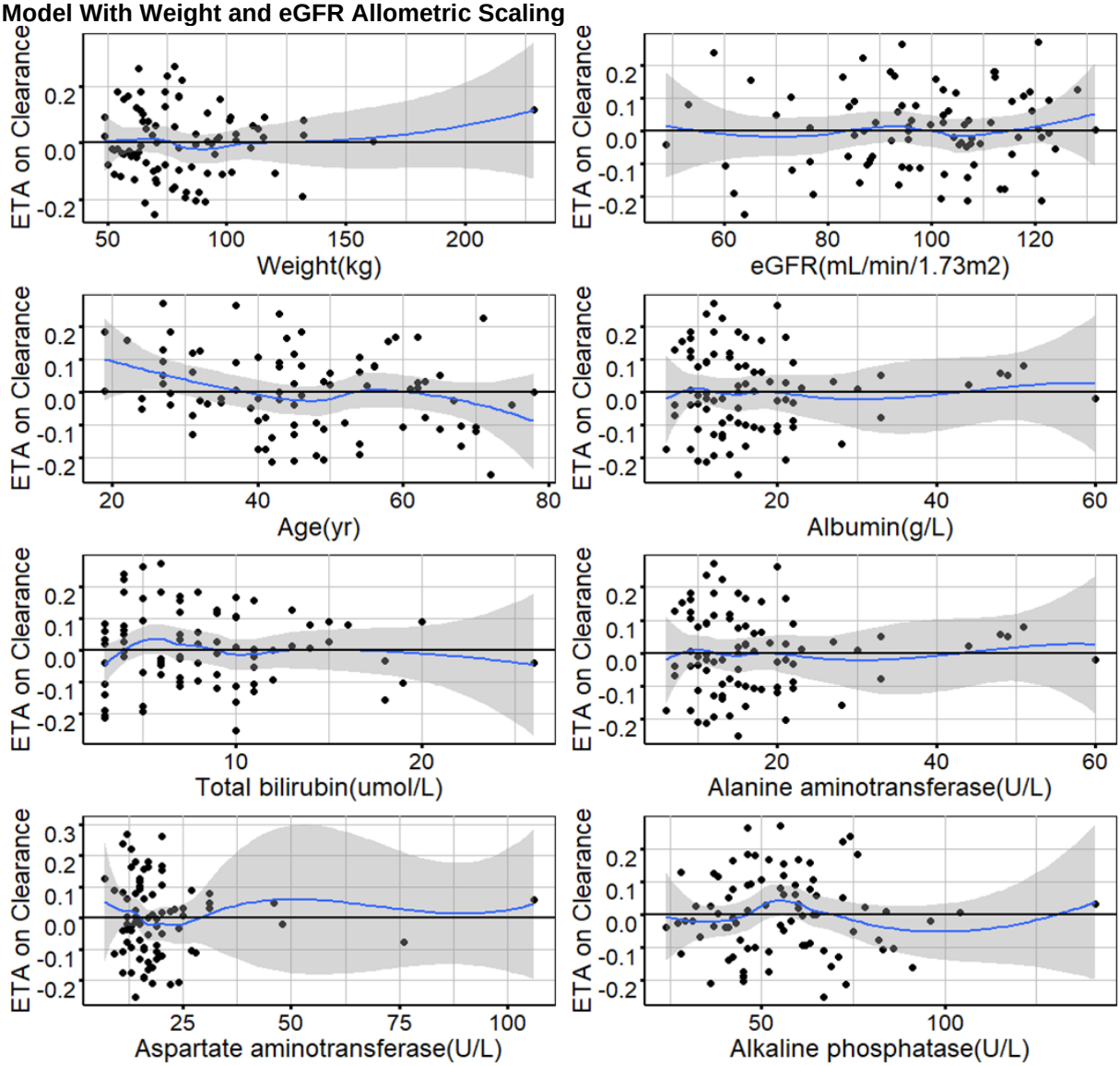
Figure 13. Covariate Effects on Final PopPK Model Parameters



Covariate	Median	95%LCI	95%UCI
EGFR 95th (122.4 mL/min/1.73m2) on CL	1.09	1.06	1.13
EGFR 5th (62.2 mL/min/1.73m2) on CL	0.81	0.75	0.86
Weight 95th (130 kg) on CL	1.15	1.10	1.20
Weight 5th (53 kg) on CL	0.91	0.88	0.94
Weight 95th (130 kg) on V	1.37	1.26	1.47
Weight 5th (53 kg) on V	0.81	0.77	0.86

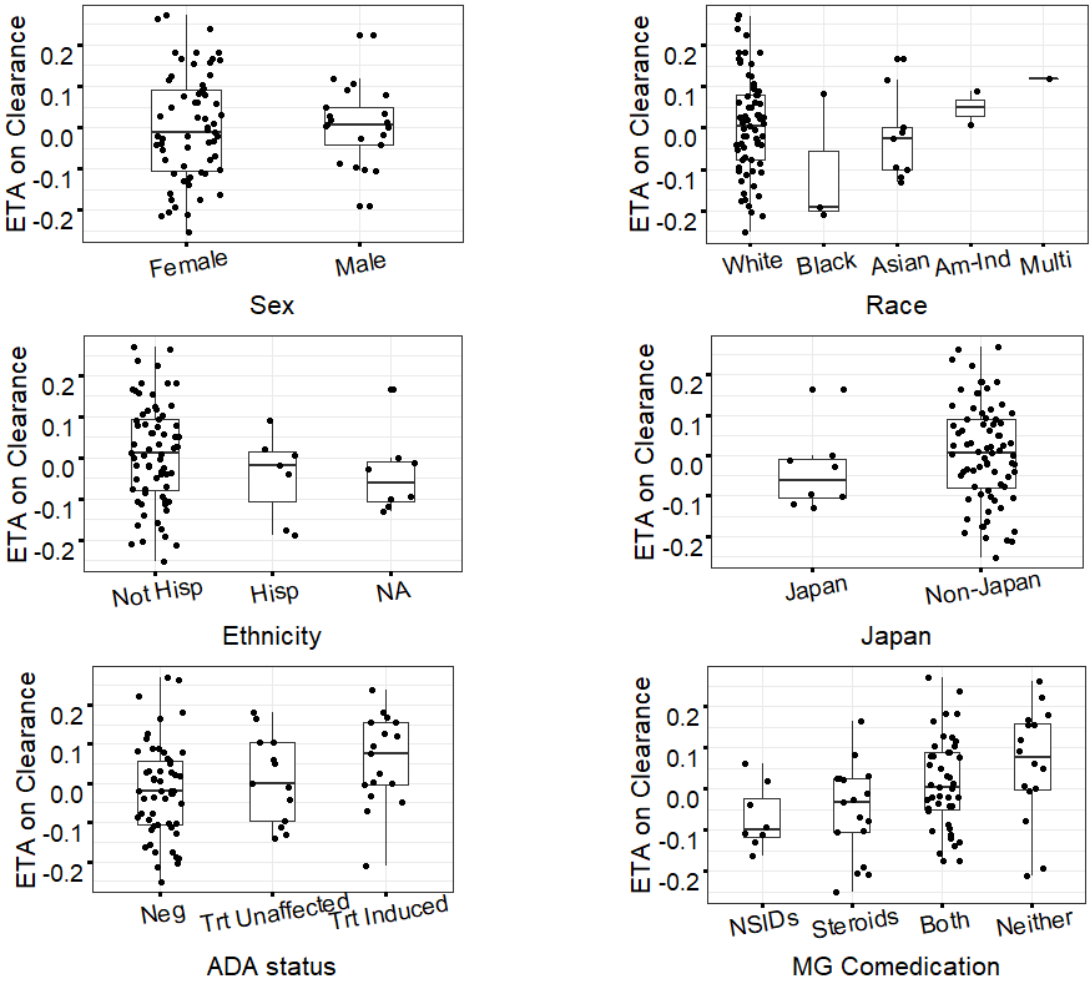
Source: Reviewer's Analysis
Abbreviations: CL, clearance; EGFR, estimated glomerular filtration rate; LCI, lower confidence interval; PopPK, population pharmacokinetics; UCI, upper confidence interval; V, volume

Figure 14. ETA Covariate Plots on Clearance Versus Continuous Covariates for Final PopPK Model With Weight and eGFR Allometric Scaling



Source: Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; ETA, interindividual variability; PopPK, population pharmacokinetics

Figure 15. ETA Covariate Plots on Clearance Versus Categorical Covariates for Final PopPK Model With Weight and eGFR Allometric Scaling

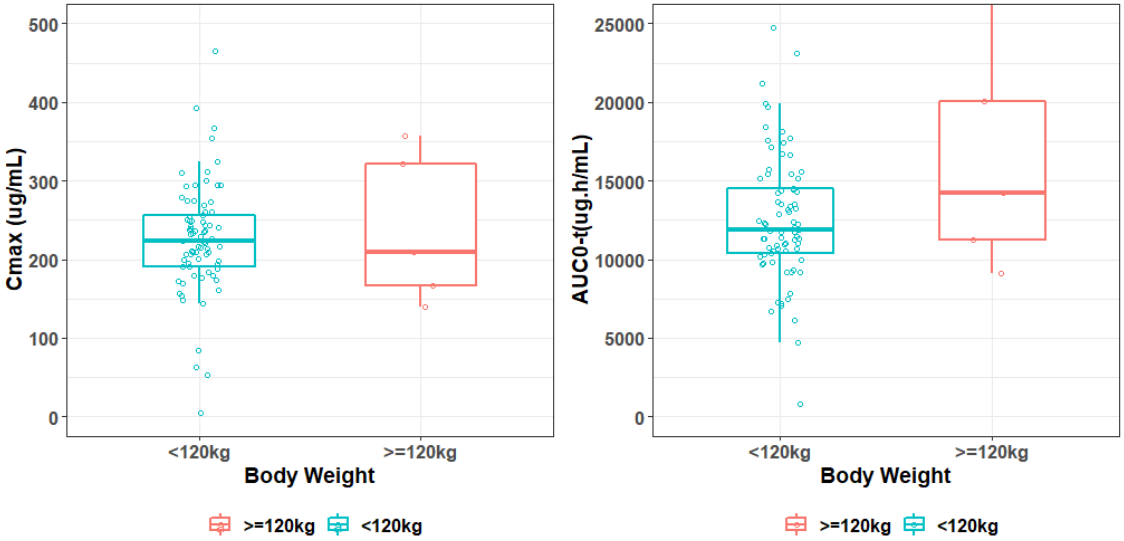


Source: Reviewer's Analysis
Abbreviations: ADA, antidrug antibody; eGFR, estimated glomerular filtration rate; ETA, interindividual variability; MG, myasthenia gravis; NA, not applicable; PopPK, population pharmacokinetics

Evaluation of Bodyweight-Based Dose Regimen

The dosage and administration section of the label states that the dose of efgartigimod required is based on the patient's body weight and the recommended dose of 10 mg/kg. For patients weighing over 120 kg, a bodyweight of 120 kg should be used. The maximum total dose per infusion is 1200 mg. Overall, the proposed capped dose of 1200 mg per infusion was shown to be reasonable. Similar C_{max} and AUC in subjects with bodyweight <120 kg and ≥120 kg were observed with proposed dosing regimen (Figure 16).

Figure 16. Comparison of C_{max} and AUC_{0-t} Across Bodyweight Subgroups (≥120 kg and <120 kg)



Group	N	Cmax	Tmax	Half-life	AUC_last	AUC_inf
<120kg	71	224.5	1.3	76.6	11965.3	12452
>=120kg	5	210.0	1.3	87.7	14228.4	14623

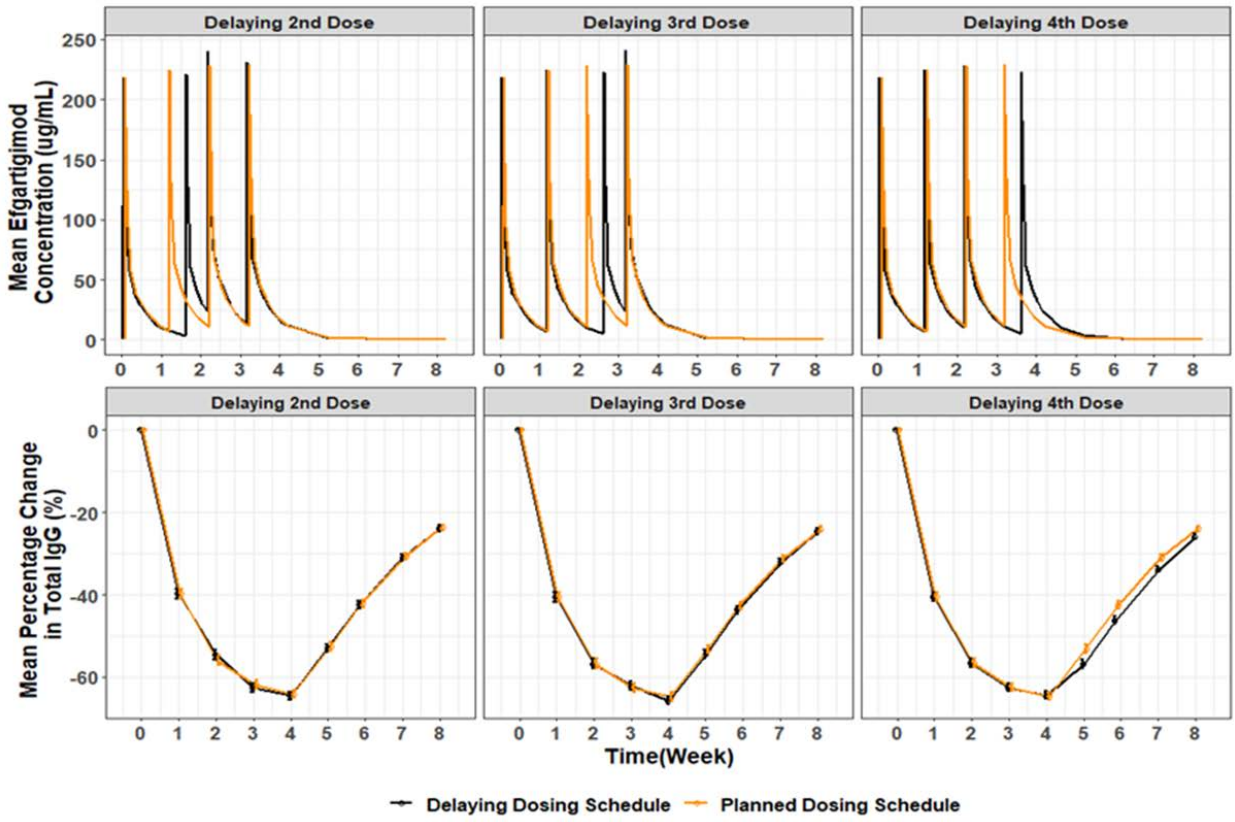
Source: Reviewer's analysis
Abbreviations: AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to Cmax

Evaluation of Proposed Dose Recommendation for Missed/Delayed Dose

The Applicant proposed that if a scheduled infusion is not possible, efgartigimod may be administered up to 3 days before or after the scheduled time point. Thereafter, resume the original dosing schedule until the treatment cycle is completed.

The reviewer conducted PK simulations to evaluate the treatment strategy after delayed dose. Simulation results show that a delayed dose for up to 3 days would not result in a significant loss in total IgG reduction. (Figure 17).

Figure 17. PK and PD Simulation of Delayed Dose Scenarios for Four Weekly IV Infusion of Efgartigimod (10 mg/kg) in a Typical gMG Patient (Bodyweight:76.05 kg, eGFR:100.27 mL/min/1.73m^2)



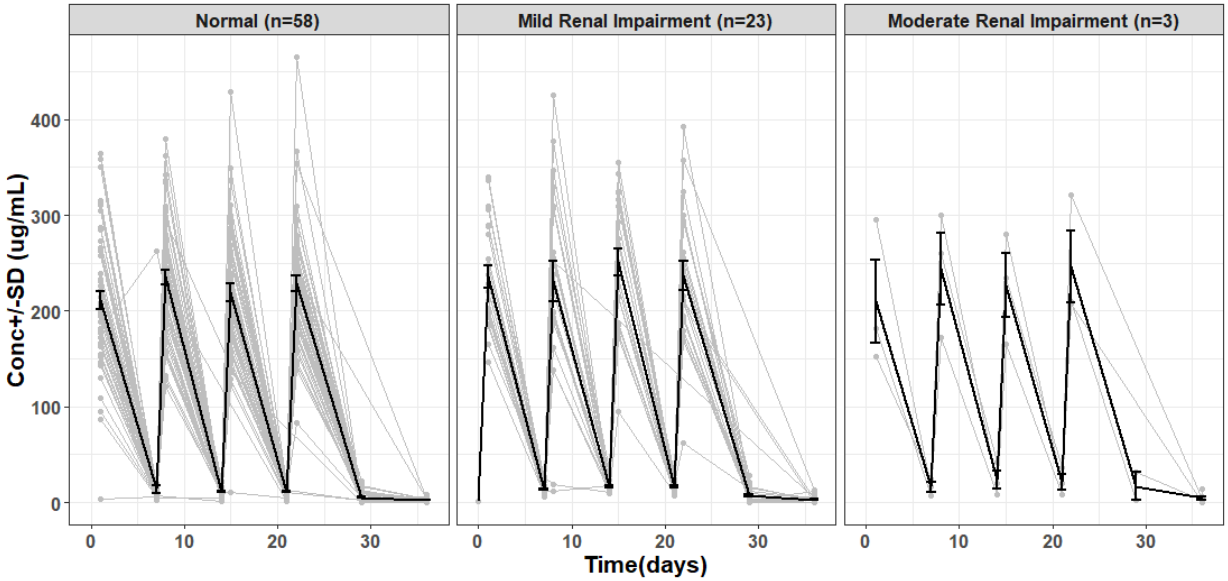
Source: Reviewer's analysis
Abbreviations: eGFR, estimated glomerular filtration rate; gMG, generalized myasthenia gravis; IgG, immunoglobin G; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic

Evaluation of Proposed Dose Regimen for Renal Impairment Patients

Figure 18 and Figure 19 show efgartigimod concentration measured predose (within 1 hour prior to start of infusion) and after the end of 1-hour infusion (within 1 hour after end of infusion) on Visits 1, 2, 3, and 4 from subjects with normal (eGFR ≥90 ml/min/1.73m^2, N=58), mildly impaired (eGFR ≥60 to <90 ml/min/1.73m^2, N=23), and moderately impaired (eGFR ≥30 to <60 ml/min/1.73m^2, N=3) renal function. Summary information of the measured concentrations on Visit 4 are provided in Table 53.

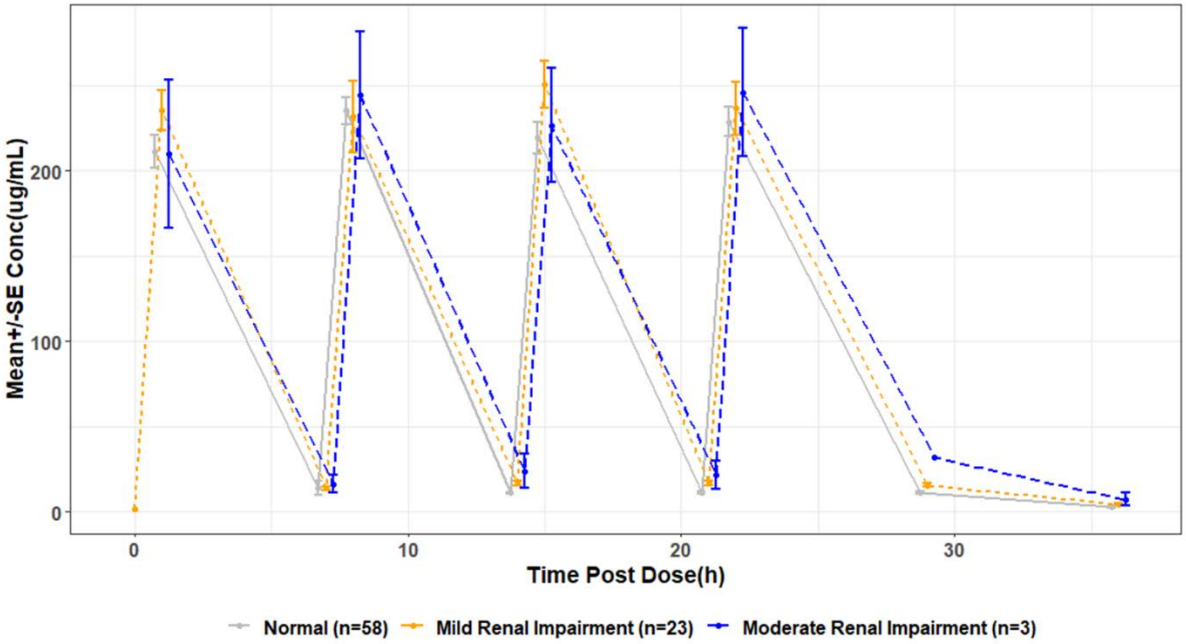
A relative AUC change of 1.22 (90%CI: 1.13, 1.30) was reported in subjects with mild renal impairment versus subjects with normal renal function based on population PK analysis. The impact of moderate renal impairment on efgartigimod AUC could not be evaluated since the data from only three subjects were available.

Figure 18. Observed Efgartigimod Serum Concentration-Time Profiles After Efgartigimod IV Infusion for 4 Weeks Stratified by Renal Function, Study 1704, Cycle 1



Source: Reviewer's analysis
Abbreviations: IV, intravenous; SD, standard deviation

Figure 19. Mean Efgartigimod Serum Concentration-Time Profiles After Efgartigimod IV Infusion for 4 Weeks, Study 1704, Cycle 1



Source: Reviewer's analysis
Abbreviations: IV, intravenous; SE, standard error

14.5.3. Listing of Analyses Codes and Output Files

Table 70. Listing of Analysis Codes and Output Files

File Name	Description	Location
pk_analysis_Efgartigimod.R	Exploratory PK analysis	M:\Review\BLA761195_Efgartigimod\PPK\Reviewer\Rscript
Forest plot.R	PopPK analysis	M:\Review\BLA761195_Efgartigimod\PPK\Reviewer\Rscript

Source: Reviewer's analysis
Abbreviations: PK, pharmacokinetic; PopPK, population pharmacokinetic

15. Trial Design: Additional Information and Assessment

Not applicable.

16. Efficacy: Additional Information and Assessment

16.1. Study 1704 Subgroup Analyses

As shown in the following table (Table 71) efgartigimod groups showed numerically larger percentages of MG-ADL responders when compared to placebo across all subgroups of age, sex, race, region, baseline MG-ADL category, and concomitant gMG treatment, except for groups of small sample size (Japan and "Other" race).

Table 71. MG-ADL Responders During Cycle 1 by Subgroup in the Overall Population, Study 1704

Subgroup Parameter	Efgartigimod n/N (%)	Placebo n/N (%)	Difference in Response % (95% CI)
Age group			
18 to <65 years	49/73 (67.1)	30/69 (43.5)	23.6 (7.7; 39.5)
≥65 years	8/11 (72.7)	1/14 (7.1)	65.6 (36.0; 95.2)
Sex			
Female	44/63 (69.8)	23/55 (41.8)	28.0 (10.7; 45.3)
Male	13/21 (61.9)	8/28 (28.6)	33.3 (6.7; 60.0)
Race			
Black or African American	3/3 (100)	1/3 (33.3)	66.7 (13.3; 100)
Asian	4/9 (44.4)	3/7 (42.9)	1.6 (-47.4; 50.6)
White	47/69 (68.1)	26/72 (36.1)	32.0 (16.4; 47.6)
Other	3/3 (100)	1/1 (100)	-
Region			
United States	20/25 (80.0)	515 (33.3)	46.7 (18.1; 75.2)
Japan	3/8 (37.5)	3/7 (42.9)	-5.4 (-55.0; 44.3)
Rest of world	34/51 (66.7)	23/61 (37.7)	29.0 (11.2; 46.7)
Concomitant gMG treatment			
NSID	33/49 (67.3)	19/49 (38.8)	28.6 (9.6; 47.5)
Non-NSID	24/35 (68.6)	12/34 (35.3)	33.3 (11.0; 55.5)
AChR-Ab status			
Seropositive	44/65 (67.7)	19/64 (29.7)	38.0 (22.1; 54.0)
Seronegative	13/19 (68.4)	12/19 (63.2)	5.3 (-24.9; 35.4)

Subgroup Parameter	Efgartigimod n/N (%)	Placebo n/N (%)	Difference in Response % (95% CI)
MG-ADL category at baseline			
5-7	11/20 (55.0)	9/22 (40.9)	14.1 (-15.87; 44.05)
8-9	22/31 (71.0)	10/34 (29.4)	41.6 (19.42; 63.69)
≥10	24/33 (72.7)	12/27 (44.4)	28.3 (4.15; 52.41)

Source: CSR Tables 14.2.1.5.3 and 14.2.1.6.2.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; N, number of subjects in group; n, number of responders; NSID, nonsteroidal immunosuppressive drug

16.2. Study 1602

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

16.2.1. Design, Study 1602

This was a randomized, double-blind, placebo-controlled, multicenter phase 2 study to evaluate the safety, efficacy, PK, PD, and immunogenicity of efgartigimod for the treatment of autoimmune MG with generalized muscle weakness.

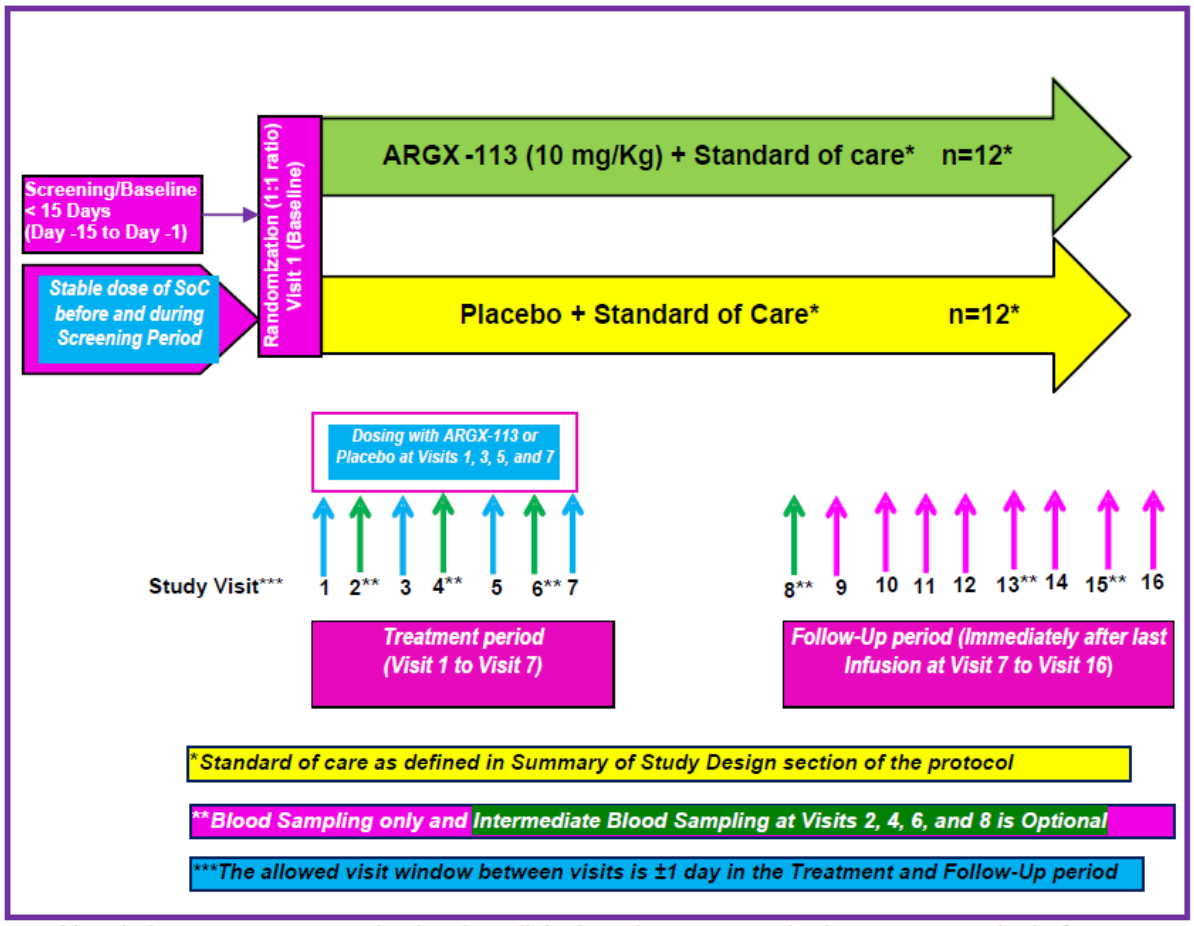
The study included a maximum screening period of 15 days, a treatment period of 3 weeks from Day 1 (Visit 1) to Day 22 (Visit 7), and a follow-up period of 8 weeks following completion of the last infusion on Day 22 (Visit 7) to Day 78 (Visit 16/Week 8 follow-up/end-of-study [EOS]).

During the treatment period, eligible subjects were randomized via a centralized Interactive Web Response System at a 1:1 ratio to receive efgartigimod (10 mg/kg) or placebo in 4 infusions administered 1 week apart in addition to their standard-of-care.

Subjects participating in this study had to be on a stable dose(s) of the standard-of-care and the dose(s) was to be maintained throughout the study without any increase or decrease. Permitted standard-of-care for MG treatment included azathioprine, other nonsteroidal immunosuppressant drugs (e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), and steroids, as well as cholinesterase inhibitors.

Thirty-five subjects consented to participate, and 24 subjects were randomized. A total of 24 subjects received 4 doses of investigational medicinal product (IMP) and reached at least 2 weeks of follow-up after last dose. Twenty-three subjects completed the study. A total of 24 subjects were analyzed for efficacy in the full analysis set and 24 subjects were analyzed for safety in the safety analysis set.

Figure 20. Study 1602 Design



Abbreviations: ARGX = Investigational Medicinal Product; n = sample size; SoC = Standard of Care.

Source: Study Protocol for ARGX-113-1602

The primary objective of this study was safety. The Applicant included some exploratory measures of efficacy using the MG-ADL, QMG, Myasthenia Gravis Composite (MGC), and a quality-of-life scale.

16.2.2. Eligibility Criteria, Study 1602

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

Key Inclusion Criteria:

- Male or female subjects aged ≥18 years
- Diagnosis of autoimmune MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III, or IVa, and likely not in need of a respirator for the duration of the study as judged by the Investigator
- A total score of ≥5 on the MG-ADL at SEB with more than 50% of this score attributed to nonocular items

- Subjects are required to be on a stable dose of their MG treatment prior to randomization

Key Exclusion Criteria:

- Females who are pregnant or lactating
- MGFA Class I, IVb, and V
- Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to screening
- Immunoglobulins given intravenously (IVIG), or intramuscular route, or plasmapheresis/plasma exchange within 4 weeks before screening
- Thymectomy when performed <3 months prior to screening

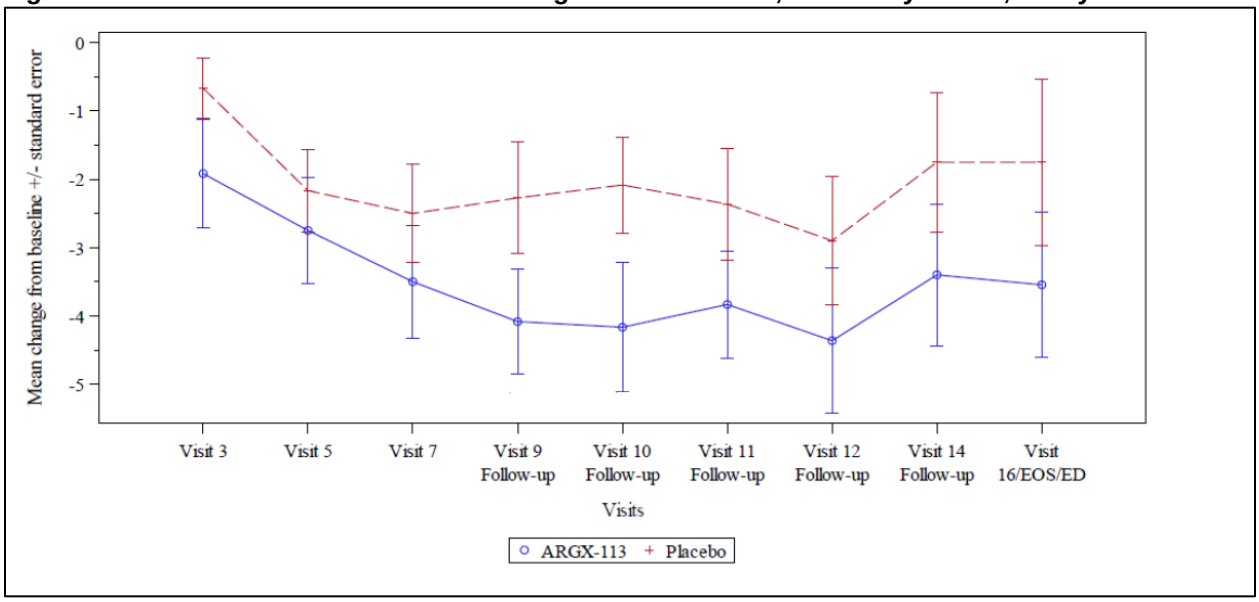
16.2.3. Statistical Analysis Plan, Study 1602

Safety, tolerability, efficacy, PK, and PD data are listed and summarized by treatment group using descriptive statistics. Graphical representations of data are presented. No formal hypothesis testing was conducted in this study; p-values, if presented, are to be interpreted descriptively.

16.2.4. Results of Analyses, Study 1602

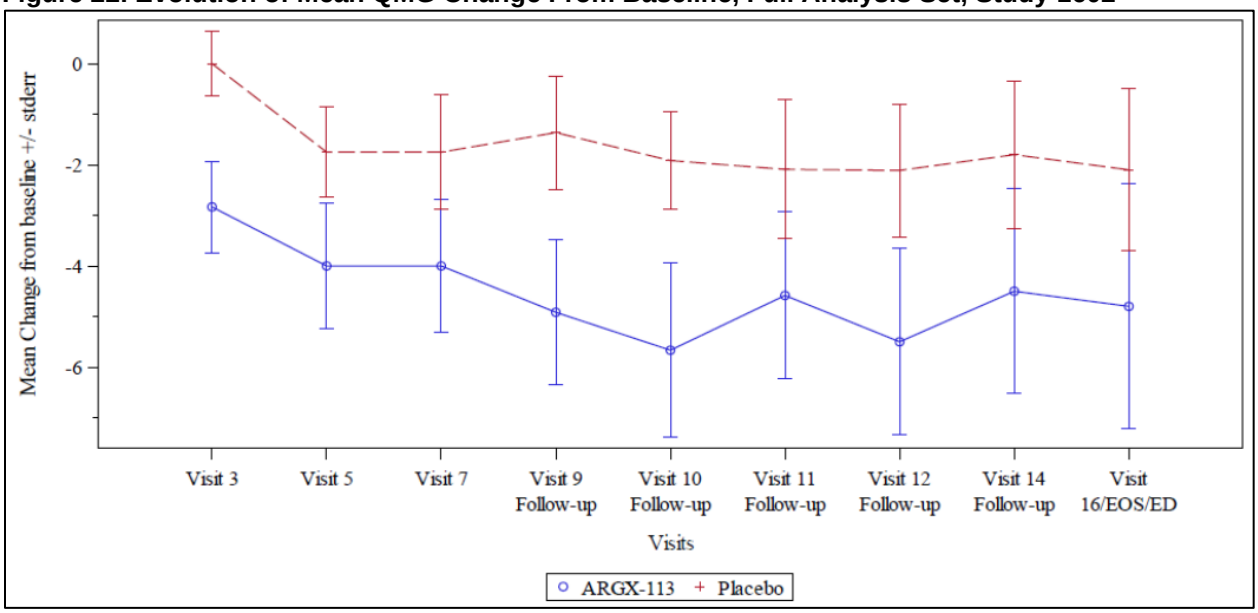
Study 1602 explored the efficacy of efgartigimod compared to placebo through change from baseline analyses on the MG-ADL (Figure 21) and the QMG (Figure 22). There were 24 subjects (12 placebo-treated and 12 efgartigimod-treated) who were randomized and treated in the study. Nominal differences favoring efgartigimod on change from baseline in MG-ADL and QMG scores compared to placebo in Study 1602 were noted through the entire double-blind period.

Figure 21. Evolution of Mean MG-ADL Change From Baseline, Full Analysis Set, Study 1602



Source: CSR Study 1602
Abbreviations: ED, early discontinuation; EOS, end of study; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living

Figure 22. Evolution of Mean QMG Change From Baseline, Full Analysis Set, Study 1602



Source: CSR Study 1602
Abbreviations: ED, early discontinuation; EOS, end of study; QMG, Quantitative Myasthenia Gravis

17. Clinical Safety: Additional Information and Assessment

17.1. Study 1705

17.1.1. Description of Study 1705

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

17.1.2. Design, Study 1705

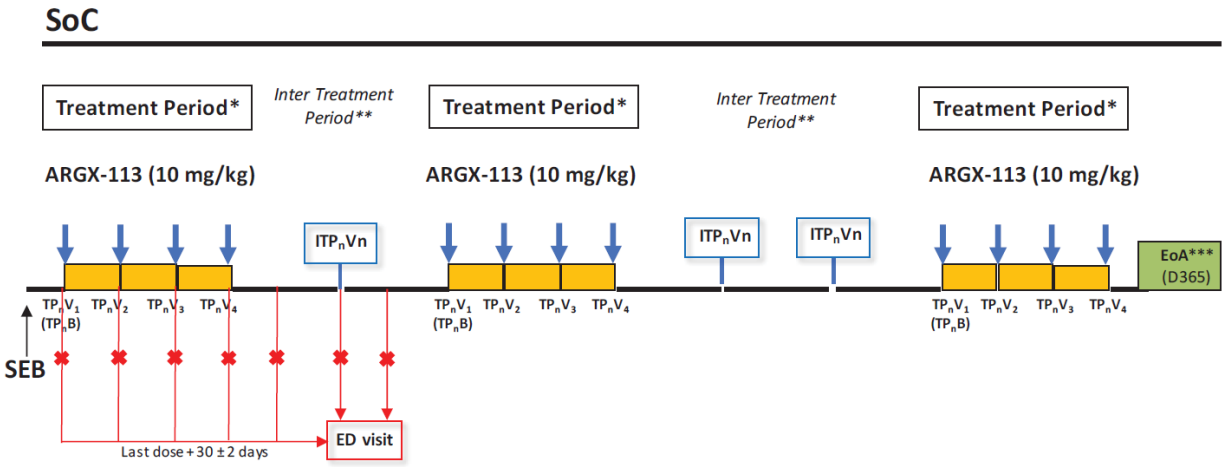
Study 1705 is a 3-year (maximum), single-arm, open-label, multicenter, phase 3 follow-on extension trial of Study 1704 to evaluate the long-term safety and tolerability of efgartigimod in subjects with gMG. A variable number of treatment periods consisting of four weekly infusions of efgartigimod (10 mg/kg of body weight) infused over a period of 3 weeks are administered to eligible subjects on an “as needed basis” in addition to their standard-of-care. The time between treatment periods is based on the duration of the treatment effect and may vary from subject to subject and within each subject from period to period. The first visit of Study 1705 coincides with the last visit of Study 1704 for each subject.

The trial consists of two parts: Part A (1 year) and Part B (up to maximum 2 years). At the end of each treatment period, subjects enter a variable intertreatment period during which they are treated with their standard-of-care only. The length of the intertreatment period may vary from subject to subject and for each subject from period to period (patient-tailored approach). For Part A, the visit frequency in the intertreatment period is every 30 days (±2 days) after the previous

visit. For Part B, the visit frequency in the intertreatment period is every 90 days (±7 days) after the previous visit.

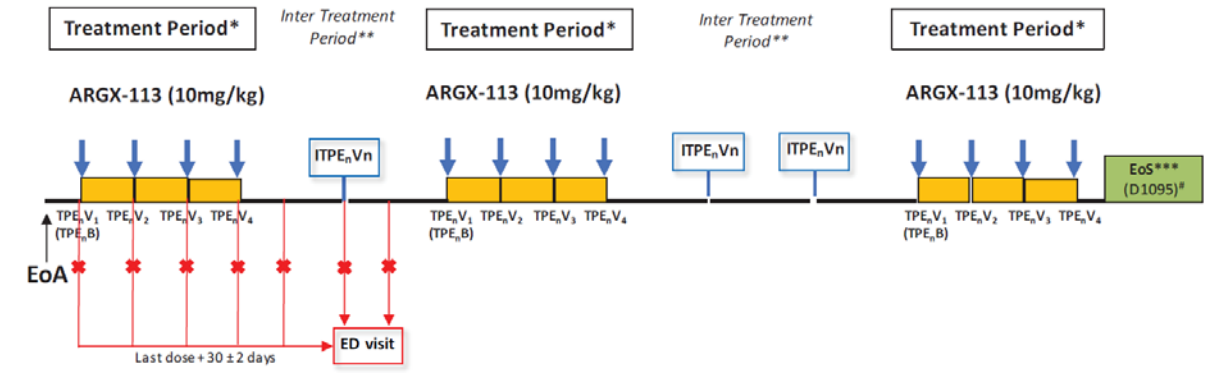
The study design is illustrated in the following figures (Figure 23 and Figure 24).

Figure 23. Study 1705 Design for Part A



Patients will be dosed on an "as needed basis".
** Weekly visits (window ±1 day) during the Treatment Periods*
***Visits every 30 days (window ±2 days) during the Inter Treatment Periods. The length between Treatment Periods may vary for each patient.*
**** EoA visit (window ± 7 days)*
ED = Early Discontinuation; EoA = End of Part A; ITP_nVn = Inter Treatment $Period_{(number)}$ Visit in Part A ; TP_nB = Treatment $Period_{(number)}$ Baseline in Part A; TP_nVn = Treatment $Period_{(number)}$ Visit in Part A; SEB = Study Entry baseline; SoC = Standard of Care
Source: CSR Study 1705

Figure 24. Study 1705 Design for Part B



Patients will be dosed on an "as needed basis".
** Weekly visits (window ±1 day) during the Treatment Periods*
***Visits every 90 days (window ±7 days) during the Inter Treatment Periods. The length between Treatment Periods may vary for each patient.*
**** EoS visit (window ± 7 days)*
#D1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first
ED = Early Discontinuation; EoA = End of Part A; EoS = End of Study; $ITPE_nVn$ = Inter Treatment $Period_{(number)}$ Visit in Part B ; TPE_nB = Treatment $Period_{(number)}$ Baseline in Part B; TPE_nVn = Treatment $Period_{(number)}$ $Visit_{(number)}$ in Part B
Source: CSR Study 1705

Overall, 167 subjects enrolled in the preceding double-blinded, placebo-controlled, phase 3, Study 1704. Of these, 151 subjects rolled over into Study 1705. At the time of the 90-Day Safety Update, 139 subjects had received at least 1 dose (or part of a dose) of open-label efgartigimod: 73 subjects were from the efgartigimod group, and 66 subjects were from the placebo group of Study 1704.

***Reviewer's comment**: The design of this open-label extension study is adequate to provide additional safety data for efgartigimod.*

17.1.3. Eligibility Criteria, Study 1705

Key Inclusion Criteria:

- Subjects who participated in Study 1704 and are eligible for roll over, i.e.,

– Subjects who reached end-of-study at Day 182 in Study 1704.
– Subjects who needed (re-)treatment in Study 1704 but cannot complete a treatment cycle within the time frame of that trial may immediately roll over into this trial to receive treatment with efgartigimod.
– Subjects who discontinued early from randomized treatment for other reasons than pregnancy, rescue therapy or an SAE in Study 1704 were offered the option to roll over into this trial.
– Subjects who had a temporary interruption from randomized treatment in Study 1704 were offered the option to roll over into this trial.

- Subjects are required to be on a stable dose of their standard-of-care MG treatment prior to SEB. The standard-of-care is limited to acetylcholinesterase (AChE) inhibitors, steroids and NSIDs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide).

Key Exclusion Criteria:

- Subjects who discontinued early from Study 1704 or subjects who discontinued early from randomized treatment for rescue or pregnancy reasons or an SAE that is likely to result in a life-threatening situation or pose a serious safety risk.
- Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing.
- Subjects with known hepatitis B virus, hepatitis C virus, or HIV seropositivity.
- Subjects with known autoimmune disease other than MG
- Subjects with clinical evidence of other significant disease or subjects who underwent a recent major surgery, which could confound the results of the trial or put the subject at undue risk.

17.2. Safety Population Across Phase 1, 2 and 3 Studies

Table 72 indicates the number of subjects enrolled across the phase 1, 2 and 3 studies by population type.

Table 72. Safety Population, Size, and Denominators

	Safety Population (N=359)	
Clinical Trial Groups	**Efgartigimod (n=246)**	**Placebo (n=113)**
Healthy volunteers	84	18
Controlled trials	96	95
Uncontrolled trials (includes new exposures in Study 1705)	66	N/A

Source: The above data are calculated from data presented in the ISS Summary of Clinical Safety submitted by the Applicant pages 14, 15, 18, and 27.
Data displayed are from the safety database for efgartigimod. Individuals exposed to any treatment in this development program for the indication of myasthenia gravis.
Abbreviations: N, total number of subjects in population; n, number of subjects in treatment group; N/A, not applicable

17.3. Exposure After the 90-Day Safety Update

Table 73. Follow-Up Duration of Subjects Exposed to at Least 1 Treatment Cycle or at Least 7 Treatment Cycles of Efgartigimod, After the 90-Day Safety Update, Pooled Studies 1602, 1704, and 1705

Number of Treatment Cycles	≥6 Months Follow-Up	≥12 Months Follow-Up	≥18 Months Follow-Up
At least 1	141	87	19
At least 7	57	48	13

Source: This table was created by the reviewer using ISS PB2 90-Day Safety Update ADAPER dataset.
For subjects who started at least X cycles, Actual Pooled Treatment Group 1 = total efgartigimod, Pooled Subject Group 1 = greater than or equal to X cycles, Grouped by USUBJID and minimum Period Start Datetime and maximum Period End Datetime; Formula: [(Period Max – Period Min)/(24*3600)] =1 where 6 months ≥182.5 days, 12 months ≥365 days, and 18 months ≥547.5 days

Table 74. Cycle Duration in Subjects With at Least X Cycles (Method 1), After the 90-Day Safety Update, Pooled Studies 1602, 1704, and 1705

	Period Duration (Days)			
Cycle	**N[1]**	**Mean (SD)**	**Min, Max**	**Median**
1	153	85 (45)	42, 415	72
2	132	82 (51)	37, 470	71
3	115	71 (34)	15, 218	58
4	92	65 (26)	4, 180	55
5	78	63 (23)	35, 156	51
6	60	60 (16)	32, 110	51
7	35	59 (14)	49, 106	54
8	18	56 (10)	44, 86	55
9	8	53 (4)	49, 57	53
10	5	52 (3)	50, 57	50
11	3	52 (4)	50, 57	50
12	1	50 (N/A)	50, 50	50

Source: This table was created by the reviewer using ISS Pb2 90-Day Safety Update ADAPER dataset
For Cycle X, Pooled Subject Group 1 = Cycle X through Cycle 13; Period C = Cycle X; Period End Date Imput. Flag = Inverse of Yes.
[1] The number of subjects that contributed to the calculation of the duration of each treatment cycle is less than the overall number of subjects who received the treatment cycle as the reviewer excluded subjects who had treatment cycles truncated by the data cut off.
Abbreviations: N, number of subjects in treatment group; SD, standard deviation

Table 75. Cycle Duration in Subjects With a Maximum of X Cycles (Method 2), After the 90-Day Safety Update, Pooled Studies 1602, 1704, and 1705

		Duration of Follow-Up (Days)			
Cycle	N	Mean (SD)	Min, Max	Median	Average Cycle Duration (Days)[1]
1	25	202 (172)	42, 554	79	79
2	10	320 (156)	116, 545	341	171
3	22	322 (142)	115, 651	305	102
4	18	352 (111)	213, 603	338	85
5	11	358 (84)	270, 498	309	62
6	19	395 (88)	282, 555	413	69
7	22	418 (99)	286, 650	407	58
8	17	469 (56)	412, 615	454	57
9	10	502 (93)	407, 658	462	51
10	3	500 (57)	466, 565	467	47
11	2	593 (35)	569, 618	593	54
12	2	617 (11)	610, 625	617	51
13	1	623 (N/A)	623, N/A	623	48

Source: This table was created by the reviewer using ISS PB2 90-Day Safety Update ADAPER dataset
[1] Based on Median Follow-Up.
Cumulative Cycle Duration in Days = [(Period End Datetime - Phase Start Datetime)/(24 x 60 x 60)] +1.
Abbreviations: N, number of subjects in treatment group; SD, standard deviation

17.3.1. Summary of Updates to Narratives in Subjects With Fatal Outcomes From the 90-Day Safety Update

Table 76 includes updates to SAEs with fatal outcome included in the 90-Day Safety Update.

Table 76. Updates to Narratives in Subjects With Fatal Outcome From the 90-Day Safety Update

Subject ID	AE Listed as Cause of Death	Update
(b) (6)	Myasthenia gravis crisis	The sponsor updated the narrative to include completion of treatment with dopamine on Day 243.
	Acute myocardial infarction	The date of the SAE of acute myocardial infarction was changed from (b) (6) to (b) (6).
	Lung neoplasm malignant	The preferred term of lung neoplasm malignant was updated to lung carcinoma cell type unspecified stage IV.

Source: Safety Reviewer
Abbreviations: AE, adverse event; SAE, serious adverse event

17.3.2. Summary of Narratives of Subjects With SAEs

Overall, the reviewer could not rule out a role for efgartigimod in SAEs related to infection given that infections were among the most frequently reported adverse event (AE) in clinical trials. Additionally, a role for efgartigimod in one event of depression could not be ruled out given absence of known risk factors.

The most frequently reported SAEs across the clinical program were SAEs related to infection (n=7), myasthenia gravis (n=6), malignancy (n=4), and diarrhea/irritable bowel syndrome (n=2).

For SAEs related to infection, the reviewer notes seven SAEs belonging to the system organ class (SOC) of Infections and Infestations reported in seven efgartigimod-treated subjects (including one subject from Study 1603). The following preferred terms were reported:

pneumonia (n=2) and coronavirus disease 2019 (COVID-19) pneumonia (n=2); COVID-19, pneumonia Escherichia, and dysentery were each reported once. The reviewer notes that a role for efgartigimod in the SAEs related to infection could not be ruled out given that infections were the most frequently reported AE in clinical trials. Additionally, treatment with efgartigimod resulted in lowering of IgG levels and was associated with reductions in leukocytes, lymphocytes, and neutrophils. Refer to Section 7.7.1 for further details.

In five of the seven SAEs, the reviewer notes the potential confounding factor of concomitant immunosuppressive medication use, including azathioprine, cyclosporine, mycophenolate mofetil, prednisolone, and prednisone (Subjects (b) (6) . In the remaining two cases, underlying risk factors of splenectomy (Subject (b) (6)) and baseline symptoms of fatigue, choking, and slurred speech (Subject (b) (6)) were confounding factors for the development of pneumonia. Refer to Section 7.6.3.2 of this review for further discussion of the case of Subject (b) (6).

For SAEs related to myasthenia gravis, preferred terms included myasthenia gravis (n=4) and myasthenia gravis crisis (n=2).

The reviewer did not identify a role for efgartigimod in five of the six cases of myasthenia gravis/myasthenia gravis crisis because of potential contributory factors or because of a lack of temporal association. Three cases had infection (pneumonia) as a potential contributory factor for worsening myasthenia gravis (Subjects (b) (6)). In the remaining 2 cases, the subjects had received at least 16 doses of efgartigimod prior to developing the SAEs ((b) (6)). In addition, the time from drug administration to event onset was separated by at least 10 days.

In the sixth case of myasthenia gravis, the exacerbation appeared to be secondary to an exacerbation of the subject's underlying myasthenia gravis. The reviewer summarizes the case here.

Myasthenia Gravis, Subject (b) (6)

A 49-year-old female with history of myasthenia gravis (diagnosed ~9 years before, MG ADL score category of severe at baseline) and restless leg syndrome was hospitalized for the SAE of myasthenia gravis on Day 9. For her first dose on Day 1, she received an overdose of 11 mg/kg rather than 10 mg/kg. On Day 3, she reported generalized weakness and fatigue. On the day of her second dose (Day 6), she had increased slurred, nasal, and hoarse speech and affected vision. She was admitted to the hospital 3 days later with difficulty swallowing, worsening facial weakness, worsening of restless leg syndrome, impaired balance, and facial rash (that was a typical part of her flares), and was treated with intravenous immunoglobulin (IVIG), methylprednisolone, paracetamol, diphenhydramine, and normal saline. She was discharged 6 days later. Two weeks later, she was readmitted for myasthenia gravis exacerbation and treated with IVIG. The SAE was considered resolved on Day 61. The study drug was permanently withdrawn because of the SAE and she did not enroll into the extension study.

Concomitant medications included prednisone, pyridostigmine, IVIG, betamethasone dipropionate, famotidine, levalbuterol, lisinopril, ondansetron, oxybutynin, paracetamol,

ropinirole, venlafaxine, warfarin, gabapentin, lidocaine, oxycodone, multivitamin, and cholecalciferol. Her past medical history also included cardiac failure, atrial flutter, atrioventricular block, hypertension, hyperlipidemia, sleep apnea, deep vein thrombosis, asthma, reflux, hypothyroidism, hypokalemia, obesity, anxiety, and depression.

***Reviewer's comment**: The case was discussed with Dr. Rainer Paine in an email communication dated June 22, 2021. Based on timing of events, the cause of the myasthenia gravis exacerbation appears consistent with an exacerbation of her underlying myasthenia gravis as the event occurred 9 days into therapy with efgartigimod. Specifically, the subject had not likely achieved maximal reduction in IgG levels, which is the proposed mechanism of action of the drug, and which was observed to occur at Week 4 in Study 1704. Refer to Section 7.7.1 on infections for a detailed description of the IgG-lowering effects of efgartigimod. Another factor supportive of the case representing an exacerbation of her underlying myasthenia gravis is that the SAE resolved 2 months after the most recent dose of efgartigimod, which has a terminal half-life listed on the proposed label by the Applicant of 3 to 5 days*

The reviewer notes one SAE of depression where the reviewer could not rule out a role for efgartigimod and summarizes the case here.

Depression, Subject [redacted] (b) (6)

A 19-year-old male with history of myasthenia gravis who was hospitalized for the SAE of depression on Day 177. He had no history of depression or psychiatric illness. On Day 128, he reported the treatment-emergent adverse event (TEAE) of depression, which was characterized by feelings of hopelessness, fatigue, and a lack of prospects for the future. He had received 8 doses of efgartigimod prior to the TEAE. The most recent dose had been the day before. He was prescribed lamotrigine, venlafaxine, mirtazapine, and sulpiride. On Day 177, he was hospitalized for the SAE of depression and reported disordered sleep, feelings of hopelessness, and sluggishness. He denied suicidal thoughts or psychotic symptoms. Concomitant medications at the time of the SAE included mycophenolate mofetil, ambenonium chloride, prednisone, omeprazole, and potassium chloride. He was treated with agomelatine and piracetam and achieved partial improvement in his mental state. He completed the study on Day 199.

***Reviewer's comment**: A role for efgartigimod in the SAE of depression cannot be ruled out given onset of the SAE while receiving efgartigimod and the subject's lack of history of psychiatric illness.*

For SAEs related to diarrhea and irritable bowel syndrome, the reviewer did not establish a role for efgartigimod because of the presence of past medical history that was likely contributory. The SAE of irritable bowel syndrome had the risk factor history of irritable bowel syndrome (Subject [redacted] (b) (6)). The SAE of diarrhea had a potential confounding factor of a diagnosis of colovesicular fistula (Subject [redacted] (b) (6)).

For SAEs related to malignancy, the reviewer notes five SAEs reported in five subjects. The following preferred terms were reported: squamous cell carcinoma of the vulva, prostate cancer, rectal adenocarcinoma, lung neoplasm malignant, and pancreatic carcinoma. The reviewer did not identify a role for efgartigimod in the events given the risk factors of age >50 years in four cases (Subjects [redacted] (b) (6)

[redacted]) and tobacco use in the fifth case (Subject [redacted]).

The reviewer did not establish a role for efgartigimod in other SAEs reported in the clinical program because of a lack of temporal association, or because of the presence of contributory factors such as past medical history. The SAE of spinal compression fracture was reported in a subject with history of osteoporosis (Subject [redacted]). The SAE of worsening anemia was reported in a subject with history of anemia (Subject [redacted]). The SAE of retinal detachment was reported in a subject with the risk factor of older age (Subject [redacted]). The SAE of bladder neck obstruction was reported in a subject with history of prostate cancer (Subject [redacted]). The SAE of thrombocytopenia occurred in a subject with history of idiopathic thrombocytopenic purpura (Subject [redacted]). The SAE of hyperventilation did not appear temporally associated with efgartigimod administration as the event was reported 6 days after drug administration (Subject [redacted]).

90-Day Safety Update

The 90-Day Safety Update included a new narrative for a subject who reported the SAE of congestive cardiac failure in the setting of atrial fibrillation with rapid ventricular rate (Subject [redacted]). In this case, a role for efgartigimod could not be established because of a likely contributing factor of atrial fibrillation, which was diagnosed prior to the subject receiving efgartigimod.

The 90-Day Safety Update also included an update to a narrative of a 62-year-old subject with the SAE of prostate cancer who subsequently developed adenocarcinoma of the colon on Day 399 after receiving 6 cycles of efgartigimod (Subject [redacted]). The reviewer did not identify a role for efgartigimod in the case given the confounding risk factor of age >50 years for the event.

The 90-Day Safety Update also included the narratives of two subjects who experienced late-breaking SAEs (defined as SAEs occurring between December 1, 2020, and February 5, 2021). In both cases, the reviewer did not identify a role for efgartigimod. In one case, the subject had a history of obstructive sleep apnea as a risk factor developing a pulmonary embolism (Subject [redacted]). In the second case, the subject reported the SAE of spinal operation after developing gluteal pain radiating into both legs 10 months after his first dose of efgartigimod and was diagnosed with high-grade spinal canal stenosis of L3/4 on magnetic resonance imaging (MRI) (Subject [redacted]).

The Applicant updated four narratives of SAEs without fatal outcome. Three of the updated narratives were related to the topic of Human Carcinogenicity and are addressed in Table 77 (Subjects [redacted]). In the remaining narrative, the reviewer did not identify a role for efgartigimod in the SAE of arrhythmia because of likely contributory factors of medical history of coronary artery disease, hypertension, first degree AV block, right bundle branch block, and sinus bradycardia (Subject [redacted]). Table 77 lists updates to the narratives of subjects with SAEs that did not result in fatal outcomes. For a review of updated narratives of SAEs with fatal outcome, refer to the Section 17.3.1 in the Appendix.

Table 77. Updates to Narratives in Subjects With SAEs Without Fatal Outcome From the 90-Day Safety Update

Subject ID	Original SAE(s) Listed	Update
(b) (6)	Thrombocytosis	The SAE of thrombocytosis was updated to myeloproliferative neoplasm.
	Squamous Cell Carcinoma of the Vulva	The narrative was updated to include the results of a biopsy that confirmed a diagnosis of vulvar spinocellular carcinoma.
	Bladder Neck Obstruction	The SAEs of Adenocarcinoma of the Colon and Colectomy were reported.
	Pharyngitis Streptococcal, Influenza	The SAE of Arrhythmia was reported.

Source: Safety Reviewer
Abbreviations: SAE, serious adverse event

17.4. Reasons for Trial Discontinuation and Treatment Discontinuation by Protocol in Studies 1704, 1602, and 1705

Study Discontinuation

Subjects in Study 1704 were required to discontinue from the trial for the following reasons: subject withdrawing consent, Investigator breaking randomization code prematurely, or Investigator deeming it to be in the best interest of the subject.

In Study 1705, trial discontinuation was required for the same conditions as noted in the Study 1704 protocol as well as: pregnancy, receipt of rescue therapy, development of an SAE likely to result in a life-threatening situation or pose a serious safety risk or taking a prohibited medication.

In Study 1602, trial discontinuation was required for the following: pregnancy, lack of efficacy as judged by the Investigator, emergency unblinding, physician decision, lost to follow-up, or request of the Sponsor. Subjects could also discontinue from the trial if there was clinical evidence of a bacterial, viral, or fungal disease or any other significant disease which could confound the results of the trial or put the subject at undue risk.

Treatment Discontinuations

In Study 1704, subjects who discontinued treatment remained in the study and continued to attend follow-up visits in the treatment cycle and at the end of treatment. Treatment discontinuation was required for the following: pregnancy, receipt of rescue therapy, development of an SAE likely to result in a life-threatening situation or pose a serious safety risk, or taking a prohibited medication (including IgG therapy, change in the type or dose/regimen of a standard of care medication, monoclonal antibody for immunomodulation, live/live-attenuated vaccines, rescue therapy when used in subjects who met the criteria to be rescued, or use of plasma exchange or immunoadsorption more than once during the study period). Treatment could also be discontinued if there was clinical evidence of a bacterial, viral, or fungal disease or any other significant disease which could confound the results of the trial or put the subject at undue risk.

Conditions noted in the Study 1704 protocol leading to treatment discontinuation also led to treatment discontinuation in Study 1705 because they were reasons for trial discontinuation.

In Study 1602, reasons for treatment discontinuation included: safety concern, disease deterioration, voluntary discontinuation from the investigational medicinal product, or major protocol deviation.

17.5. TEAEs in Study 1704

The following tables (Table 78 and Table 79) list TEAEs by preferred term and by groups of preferred terms, or by U.S. Food and Drug Administration (FDA) Medical Dictionary for Regulatory Activities (MedDRA) Query occurring with a frequency higher than placebo and of at least 5% in the efgartigimod arm in Study 1704.

Table 78. Treatment-Emergent Adverse Events[1] Occurring at Least 5% in the Efgartigimod Arm and Higher Frequency Than Placebo, Phase 3 Safety Population, Study 1704

Preferred Term[2]	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Upper respiratory tract infection	9 (11)	4 (5)
Urinary tract infection	8 (10)	4 (5)
Myalgia	5 (6)	1 (1)
Bronchitis	5 (6)	2 (2)

Source: Clinical Safety Reviewer
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event

Table 79. Groups of Preferred Terms and FDA MedDRA Queries[1] Occurring at Higher Frequency in Treatment Arm Than Placebo, Phase 3 Safety Population, Study 1704

Groups of Preferred Terms or FDA MedDRA Query	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Respiratory tract infection	28 (33)	24 (29)
Bronchitis	5 (6)	2 (2)
Chronic sinusitis	0	1 (1)
Influenza	3 (4)	3 (4)
Nasopharyngitis	10 (12)	15 (18)
Pharyngitis	1 (1)	0
Pneumonia	1 (1)	0
Respiratory tract infection	0	1 (1)
Sinusitis	2 (2)	0
Upper respiratory tract infection	9 (11)	4 (5)
Viral pharyngitis	1 (1)	0
Viral tracheitis	1 (1)	0
Headache FDA narrow	27 (32)	24 (29)
Procedural headache	4 (5)	1 (1)
Migraine	2 (2)	0
Headache	24 (29)	23 (28)
Post-traumatic headache	0	1 (1)

Groups of Preferred Terms or FDA MedDRA Query	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Paresthesia FDA narrow	6 (7)	4 (5)
Hypoesthesia	2 (2)	0
Hyperesthesia	1 (1)	0
Hypoesthesia oral	1 (1)	0
Paresthesia	2 (2)	4 (5)
Hemorrhage FDA narrow	5 (6)	3 (4)
Hematoma	1 (1)	0
Menorrhagia	1 (1)	0
Contusion	2 (2)	2 (2)
Subcutaneous hematoma	1 (1)	1 (1)
Arthralgia FDA broad	5 (6)	3 (4)
Arthralgia	2 (2)	1 (1)
Neck pain	2 (2)	1 (1)
Musculoskeletal stiffness	1 (1)	1 (1)

Source: Clinical data scientist Dr. Ling Cao
[1] Treatment-emergent adverse event defined as any AE temporally associated with the use of the investigational medicinal product (IMP), whether considered related to the IMP or not.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

For labeling purposes, the reviewer did not include the Arthralgia FDA broad group as it consisted of a broad scope of preferred terms. The reviewer did not include the following preferred terms in the FDA MedDRA Query grouped analyses as they occurred at equal or lower frequency in subjects who received efgartigimod compared to placebo: contusion, post-traumatic headache, and subcutaneous hematoma. As a result, Hemorrhage FDA narrow no longer met criteria for inclusion in the table.

For the group of Paresthesia, although the preferred term paresthesia occurred with lower frequency in the efgartigimod group compared to placebo, the preferred term was considered to be relevant to the overall group and therefore was not excluded from the group.

The group Headache included the preferred term procedural headache, which was reported in four efgartigimod-treated subjects compared to one placebo-treated subject in Study 1704. The AEs occurred within 6 to 48 hours after dosing. Verbatim terms for efgartigimod-treated subjects included “mild headache at day of last infusion,” “headache after IP administration,” “headaches occurring after each infusion and lasting until the next day,” and “headache at top left of head…occurs right after infusion.” Most of the headaches were mild and did not require additional treatment. Subjects had received between one and five doses of efgartigimod prior to reporting the headaches. Refer to Section 7.7.4 for further discussion of procedural headache in Trials 1704, 1602, and 1705.

17.6. IgG Levels and Risk for Infection

Based on the available literature, the reviewer found that the IgG level at which an individual is at risk for infection varies by individual. For example, one publication recommended that treatment with immunoglobulin therapy for primary immunodeficiency disease be individualized and guided by the IgG level at which point an individual no longer experiences infections (Shapiro et al. 2017). A review noted that patients with primary immunodeficiency syndromes and IgG levels of less than 1000 mg/L for prolonged periods have an increased risk of recurrent

infection (Furst 2009). Additionally, maintenance of IgG levels to approximately 5000 mg/L in patients with hypogammaglobulinemia reduces the risk of infection to background levels; however, higher levels of IgG may be necessary for patients with other comorbidities. In a cohort study, 5 hypogammaglobulinemia patients with IgG levels less than 3000 mg/L did not undergo treatment with immunoglobulin therapy and did not develop severe infection over the course of the length of the study (mean observation period of 11 years) (Ameratunga et al. 2019). Finally, in a published report, two patients with common variable immunodeficiency required IgG trough levels of 8000 mg/L and 9000 mg/L for intravenous immunoglobulin therapy in order to prevent recurrent infections (Bonagura et al. 2008).

17.7. TEAEs Belonging to the SOC of Infections and Infestations With Higher Frequency in the Efgartigimod Arm Compared to Placebo in Pooled Studies 1704 and 1602

Table 80 shows TEAEs belonging to the SOC of Infections and Infestations from pooled Studies 1704 and 1602.

Table 80. TEAEs Belonging to the SOC of Infections and Infestations With Higher Frequency in Efgartigimod 10 mg/kg Arm Compared to Placebo, Pooled Studies 1704 and 1602

Preferred Term	Efgartigimod 10 mg/kg (N=96) n (%)	Placebo (N=95) n (%)
Subjects with at least one TEAE belonging to the SOC infections and infestations	32 (33)	24 (25)
Upper respiratory tract infection	7 (7)	1 (1)
Urinary tract infection	8 (8)	2 (2)
Bronchitis	4 (4)	1 (1)
Ear infection	1 (1)	0
Gingivitis	1 (1)	0
Herpes zoster	1 (1)	0
Influenza	2 (2)	1 (1)
Nail bed infection	1 (1)	0
Oral herpes	1 (1)	0
Pharyngitis	1 (1)	0
Pneumonia	1 (1)	0
Sinusitis	1 (1)	0
Viral tracheitis	1 (1)	0

Source: This table was created by the reviewer using ISS ADAE pb1 dataset
Treatment-emergent analysis flag = Y; Primary System Organ Class = Infections and Infestations; Group by Unique Subject Identifier, Actual Treatment, and Dictionary-derived term.
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

17.8. TEAEs Belonging to the SOC of Infections and Infestations in Pooled Studies 1704, 1602, and 1705

Table 81 shows TEAEs belonging to the SOC of Infections and Infestations from pooled Studies 1704, 1602, and 1705.

Table 81. TEAEs Belonging to the SOC of Infections and Infestations Occurring With Frequency of at Least 2%, Pooled Studies 1704, 1602, and 1705.

Preferred Term	Efgartigimod 10 mg/kg (N=162) n (%)
Subjects with at least one TEAE	88 (54)
Nasopharyngitis	23 (14)
Urinary tract infection	15 (9)
Upper respiratory tract infection	12 (7)
Bronchitis	7 (4)
Herpes zoster	5 (3)
Influenza	5 (3)
COVID-19	4 (2)
Oral herpes	4 (2)
Pharyngitis	4 (2)
Respiratory tract infection	4 (2)
Cystitis	3 (2)
Gastroenteritis	3 (2)
Pneumonia	3 (2)

Source: This table was created by the reviewer using ISS ADAE pb2 90 Day Safety Update dataset
Treatment-emergent analysis flag = Y; Primary System Organ Class = Infections and Infestations; Group by Unique Subject Identifier, Actual Treatment, and Dictionary-derived term.
Abbreviations: COVID-19, coronavirus disease 2019; N, number of subjects in group; n, number of subjects with adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

17.9. Vital Signs

The reviewer did not identify a safety signal in analyses of vital signs. The reviewer evaluated mean change from baseline, outlier shift analyses from normal-to-high and normal-to-low, and TEAEs belonging to the SOC Investigation related to vital signs.

The reviewer did not identify any clinically significant changes in analyses of mean change from baseline of vital signs because of small magnitudes of change or because of increased variability seen in smaller sample sizes at visits towards the end of treatment cycles in Study 1704, pooled Studies 1704 and 1602, and pooled Studies 1704, 1602, and 1705. Of note, the Applicant used different vital sign categories than those specified in Attachment 1 of the pre-BLA meeting minutes dated August 26, 2020. The reviewer included results of vital sign shift analyses based on the categories specified in Attachment 1 of the meeting minutes.

Shifts to high or low categories with frequency of at least 5% higher in the efgartigimod arm compared to placebo occurred with systolic blood pressure >140 mm Hg (17% versus 12%, respectively) and body weight decrease of at least 7% from baseline (11% versus 6%, respectively) in Study 1704. There were no shifts in systolic blood pressure to >160 mm Hg greater than 1% between efgartigimod and placebo arms in Study 1704. In pooled Studies 1704 and 1602, no vital sign categories had a frequency of at least 5% higher in the efgartigimod arm compared to placebo.

In pooled Studies 1704, 1602, and 1705, vitals sign shifts with greatest frequency were diastolic blood pressure >90 mm Hg (27%), systolic blood pressure >140 mm Hg (18%), and heart rate <60 beats per minute (17%). These vital sign categories had similar frequencies in pooled Studies 1704, 1602, and 1705 as compared to Study 1704 (difference no greater than 5%).

A review of TEAEs related to vital signs showed no AEs in the efgartigimod arm with frequency higher than 5% in Study 1704, pooled Studies 1704 and 1602, and pooled Studies 1704, 1602, and 1705.

17.10. Electrocardiograms

The reviewer did not identify a safety signal in analyses of electrocardiograms (ECGs). The reviewer evaluated mean change from baseline and outlier shift analyses from normal-to-high and normal-to-low for the ECG parameters of heart rate, PR interval, QRS duration, and QT interval using Fridericia's Correction (QTcF).

The reviewer did not identify any clinically significant changes in analyses of mean change from baseline in ECG values because of small magnitudes of change or because of increased variability seen in smaller sample sizes at visits towards the end of treatment cycles in Study 1704, pooled Studies 1704 and 1602, and pooled Studies 1704, 1602, and 1705.

No ECG outlier shifts with frequency of 5% higher in the efgartigimod arm compared to placebo were observed in Study 1704 or pooled Studies 1704 and 1602. In pooled Studies 1704, 1602, and 1705, a similar frequency of ECG outlier shifts was observed compared to Study 1704 (difference no greater than 5%).

No TEAEs belonging to the SOC Investigation were related to ECG changes in Studies 1704, 1602, or 1705.

17.11. QT

A dedicated QT study was not conducted for this Fc fragment monoclonal antibody, which agreed with recommendations provided by the Office of Clinical Pharmacology in a review of IND 131153 dated April 17, 2019, and was also in accordance with International Conference on Harmonisation E14 guidelines for monoclonal antibodies that have a low likelihood of direct ion channel interactions.

The reviewer did not identify a safety signal for prolonged QTcF intervals in analyses of ECGs. The reviewer evaluated mean change from baseline and outlier shift analyses for QTcF intervals.

In Studies 1602, 1704, and 1705, no subjects had a postbaseline QTcF value of >500 milliseconds (ms).

In Studies 1602, 1704, and 1705, two subjects had a postbaseline QTcF increase of >60 ms (Subjects (b) (6)). Neither subject reported AEs related to a prolonged QT interval (such as sudden death, syncope, arrhythmia, or seizure).

In Study 1704, a similar frequency of subjects with increased QTcF intervals and categorical increases in QTcF from baseline was observed in both the efgartigimod and placebo arms. Similar findings were observed in pooled Studies 1704 and 1602. Table 82 shows the frequency of subjects with increased QTcF intervals in Study 1704.

Table 82. Frequency of Subjects With Increased QTcF Intervals, Study 1704

QTcF Intervals	Efgartigimod (N=84) n (%)	Placebo (N=83) n (%)
Length of increased QTcF intervals		
450 to 480 (msec)	6 (7)	8 (10)
480 to 500 (msec)	1 (1)	0
Increase from baseline		
30 to 60 (msec)	13 (15)	14 (17)
>60 (msec)	0	1 (1)

Source: Clinical Safety Reviewer
Abbreviations: N, number of subjects in group; n, number of subjects with increased QTcF interval

A similar frequency of subjects with QTcF interval increases >450 ms was observed in pooled Studies 1704, 1602, and 1705 compared to Study 1704 (difference no greater than 5%). A higher frequency of subjects in pooled Studies 1704, 1602, and 1705 had QTcF interval increases above baseline of 30 to 60 ms compared to Study 1704 (23% versus 15%, respectively). The frequency of subjects in Study 1705 with QTcF interval increases above baseline of 30 to 60 ms was 19%. In part, the higher frequency is likely due to the longer duration of Study 1705.

No efgartigimod-treated subjects in Study 1704 experienced a TEAE related to arrhythmia compared to three subjects on placebo (4%). No subjects in Study 1602 experienced a TEAE related to arrhythmia. In Study 1705, four subjects experienced TEAEs related to arrhythmia (frequency of 2% for pooled Studies 1602, 1704, and 1705). One subject (Subject (b) (6)) in Study 1705 with QTcF length increase of >450 ms or QTcF increase greater than 30 ms above baseline experienced an SAE of arrhythmia (verbatim term: arrhythmia, conduction defect) and had underlying risk factors including history of coronary artery disease, first degree AV block, right bundle branch block, and bradycardia. Refer to Section 17.3.2 for further details on the case.

17.12. Immunogenicity

Overall, a higher frequency of subjects with treatment-induced ADA levels was observed in the efgartigimod arm compared to placebo in Study 1704 (20% versus 7%, respectively). Because of the low number of subjects with treatment-induced ADA responses across Studies 1704, 1602, and 1705 (n=25), the reviewer did not find the database to be useful in assessing the role of efgartigimod immunogenicity on safety.

The immunogenicity of efgartigimod was assessed through the detection of ADA antibodies using an in vitro assay. The Applicant also assessed the neutralizing capacity for confirmed ADA-positive samples. Refer to the review by the Office of Biotechnology Products (OBP) for further details on the adequacy of the assays used to evaluate the immunogenicity of efgartigimod.

In Study 1704, ADA samples in the first treatment cycle were collected at baseline and on Days 22, 36, and 57. After the first treatment cycle, ADA samples were collected on Days 1 and 57 of the corresponding treatment cycles.

In Part A (first year) of Study 1705, ADA samples were collected on Days 1 and 22, and at the end of study visit. In Part B of Study 1705, ADA samples were collected at early discontinuation.

In Study 1602, ADA samples were collected at baseline and on Days 15, 22, 29, 36, 43, 50, 64, and 78.

The reviewer noted that the Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019) recommends obtaining pretreatment samples, samples at multiple intervals throughout the trial, and samples at approximately five half-lives after last exposure (~25 days given efgartigimod's half-life of 3 to 5 days as per the Applicant's proposed label). The Guidance also recommends sampling at 9 to 14 days after the first exposure to detect an IgM response. The Applicant sampled on Day 1 and then on Day 22 in Study 1704 and Part A of Study 1705, which would allow for detection of an IgG response, but not an IgM response in those trials.

ADA samples were evaluated using a 3-tier approach that included a screening ADA assay, a confirmatory ADA assay for positive screens, and a titration ADA assay for confirmed positive screens.

Table 83 shows ADA subject category definitions.

Table 83. ADA Subject Category Definitions

Subject Category		Definition
ADA evaluable	Treatment-induced ADA	Negative ADA at baseline and subsequent positive ADA after initial drug administration
	Treatment-boosted ADA	Positive ADA at baseline with 4-fold higher titer postbaseline compared to baseline.
	ADA negative	Baseline and postbaseline ADA negative
	Treatment-unaffected ADA	Positive ADA at baseline without a 4-fold higher titer postbaseline
ADA unevaluable		Subject who did not meet one of the four classifications above (due to not having an ADA evaluable sample at baseline or postbaseline or because of partial ADA results due to an incomplete 3-tiered evaluation)

Source: Protocols Study 1704 and 1705
Abbreviations: ADA, antidrug antibody

In up to 26 weeks of treatment in Study 1704, a higher frequency of subjects with treatment-induced ADA was observed in the efgartigimod arm compared to placebo (20% versus 7%, respectively).

Table 84 shows the frequency of ADA subject categories in Study 1704.

Table 84. ADA Subject Categories, Study 1704[1]

ADA Subject Category	Efgartigimod (N=83) n (%)	Placebo (N=82) n (%)
ADA negative	53 (64)	64 (78)
Treatment-induced ADA	17 (20)	6 (7)
Treatment-unaffected ADA	13 (16)	12 (15)
Treatment-boosted ADA	0	0

Source: The reviewer created this table using the 1704 ADIS dataset,
[1] The denominator is based on ADA evaluable subjects.
Parameter = subject classification for ADA overall.
Abbreviations: ADA, antidrug antibody; N, number of subjects in treatment group; n, number of subjects in ADA group

In Study 1602, treatment-induced ADA responses were recorded in four subjects in the efgartigimod arm (33%) compared to no subjects on placebo.

Table 85 shows ADA subject categories in Study 1602.

Table 85. ADA Subject Categories, Study 1602[1]

ADA Subject Category	Efgartigimod (N=12) n (%)	Placebo (N=10) n (%)
ADA negative	4 (33)	8 (80)
Treatment-induced ADA	4 (33)	0
Treatment-unaffected ADA	4 (33)	2 (20)
Treatment-boosted ADA	0	0

Source: The reviewer created this table using the 1602 ADABA dataset,
[1] The denominator is based on ADA evaluable subjects.
For ADA negative and treatment-induced: analysis visit = overall, selected flag of Baseline Value Analysis C = negative screen. For treatment unaffected, analysis visit = visit 1, analysis value category 1 = positive.
Abbreviations: ADA, antidrug antibody; N, number of subjects in treatment group; n, number of subjects in ADA group

In up to 85 weeks of treatment in pooled Studies 1704, 1602, and 1705, treatment-induced ADA responses occurred in 16% of subjects. Table 86 shows ADA subject categories in pooled Studies 1704, 1602, and 1705.

Table 86. ADA Subject Categories, Pooled Studies 1704, 1602, and 1705[1]

ADA Subject Category	Efgartigimod (N=161) n (%)
ADA negative	104 (65)
Treatment-induced ADA	25 (16)
Treatment-unaffected ADA	30 (19)
Treatment-boosted ADA	2 (1)

Source: The reviewer created this table using the Pb2 90-Day Safety Update ADIS dataset (October cutoff),
[1] The denominator is based on ADA evaluable subjects.
Parameter = subject classification for ADA overall.
Abbreviations: ADA, antidrug antibody; N, number of subjects in treatment group; n, number of subjects in ADA group

Because of the few treatment-emergent ADA responses observed, the frequency of TEAEs overall, and the frequency of TEAEs in treatment-induced ADA-positive subjects (observed in 14 of 17 efgartigimod-treated subjects and all placebo-treated subjects in Study 1704), it is not possible to determine the role, if any, of ADA antibodies in the occurrence of TEAEs.

Because of the low number of subjects who developed neutralizing antibodies, a role for neutralizing antibodies in the occurrence of TEAEs could not be established. In Study 1704, 7% (6/83) of efgartigimod-treated subjects developed neutralizing antibodies. In pooled Studies 1704 and 1705, the incidence of neutralizing antibodies was 4% (6/149). Neutralizing antibody data were not collected in Study 1602.

17.13. Inter-Center Consultation Memorandum on Vaccination in the Setting of Efgartigimod Therapy

Inter-Center Consultation Memorandum

Date: August 5, 2021

To: Michael Mathews

Center for Drug Evaluation and Research (CDER) / Office of New Drugs (OND) / Office of Regulatory Operations (ORO) / Division of Regulatory Operations for Neuroscience (DRON)

Re: BLA 761195 Efgartigimod BLA 761195

Sponsor: Argenx

From: Soumya Chatterjee, MD Center for Biologics Evaluation and Research (CBER), Office of Vaccine Research and Review (OVRR), Division of Vaccines and Related Product Applications (DVRPA)

Through: Rebecca Reindel, MD, Team Leader, CBER/OVRR/DVRPA

Through: Andrea Hulse MD, Branch Chief, CBER/OVRR/DVRPA

ICCR Submitted Date: 1/25/2021

ICCR Due Date: 10/27/2021

Consultation request from CDER:

CDER has submitted an inter-center consult request for CBER/OVRR review. Materials provided for the consultation review included a clinical overview, the proposed label, summary of clinical pharmacology, and safety and efficacy data.

CDER consult questions

- Please make recommendations regarding the appropriate timing of vaccination with respect to the end of a treatment cycle with efgartigimod.
- Please comment on the utility of checking antibody titer levels to confirm effectiveness of vaccination in subjects who received an inactivated vaccine while between treatment cycles with efgartigimod.
- Please comment on whether any postmarketing requirements would address outstanding questions that could help inform decision-making regarding vaccination and efgartigimod treatment.

Background

MG is an autoimmune disease affecting the neuromuscular junction that manifests in clinical symptoms, such as dyspnea, dysphagia, diplopia, dysarthria, ptosis, and fatigable muscle weakness. Symptoms often fluctuate in severity, generally increase with repetitive activity, and improve with rest. It is estimated that this disorder affects ~60,000 people in the United States (Sanders and Guptill 2014). Patients with mild disease experience ocular symptoms of diplopia and intermittent ptosis, and, on the other end of the spectrum, patients with severe disease experience generalized weakness that can progress into myasthenic crisis resulting in respiratory insufficiency and need for ventilatory support. The key molecules in the neuromuscular junction that are targeted by the IgG autoantibodies include AChR, muscle-specific kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LRP4). Pathogenic actions of IgG autoantibodies include functional blockade of AChR, accelerated internalization and degradation of AChR, and activation of the complement system. These pathogenic actions result in reduced density of functional AChR and simplification of the neuromuscular junction, leading to failure

of neuromuscular transmission. Anti-AChR autoantibodies are of the IgG1 and IgG3 subtypes. Anti-MuSK autoantibodies are IgG4 subtype and do not activate the complement pathway. In approximately 90% of subjects, IgG autoantibodies are detected in the serum, with the most common being against AChR. The remaining 10% of subjects may have autoantibodies that are either undetectable, at a concentration less than the assay's lower limit of detection, or against epitopes undetectable in the assay or that bind an unknown target.

A novel potential treatment approach is targeting the neonatal Fc Receptor (FcRn). FcRn mediated IgG recycling accounts for passive short-term humoral immunity that is provided in utero from mother to offspring. FcRn has a specific role in IgG homeostasis and recycles all IgG subtypes (IgG1, IgG2, IgG3, IgG4), rescuing them from lysosomal degradation. This FcRn-mediated recycling accounts for the longer half-life and higher plasma concentrations of IgGs compared to other immunoglobulins that are not recycled by FcRn (approximately 21 days for IgGs compared to approximately 5 to 6 days for IgM, IgE, IgA, and IgD).

Reviewer's comment*: Immunoglobulins, such as IgM, are not involved in FcRn mediated recycling and as such, generation and maintenance of IgM responses after vaccination is not expected to be altered with use of FcRn antagonists. Additionally, the generation of IgG responses is not expected to be altered (Nixon et al. 2015).*

Efgartigimod is an investigational human IgG1 antibody Fc fragment bioengineered for affinity to FcRn, and a first-in-class FcRn antagonist that is being developed for the treatment of patients with gMG, a severe autoimmune disease mediated by pathogenic IgG autoantibodies. Efgartigimod binds to FcRn, resulting in degradation of circulating disease-causing pathogenic IgG antibodies. The dose and schedule as per the proposed label are as follows:

- 10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks.
- Retreat subjects with treatment cycles of weekly infusions for 4 weeks according to clinical evaluation.

Reviewer's comment*: The current primary safety considerations with anti-FcRn therapies focus on the role of FcRn binding of albumin and the potential clinical implications of a reduction in serum albumin levels. Modest post-treatment reductions in albumin have been observed in preclinical studies and early phase studies in humans. However, to date, there have been no reported adverse clinical effects observed in the human clinical trials. In addition, severe depletion of IgG could theoretically increase the risk of infection. However, IgA, IgD, IgE, and IgM are not dependent on FcRn-mediated recycling and preliminary studies of another FcRn inhibitor have not demonstrated any effect on the frequencies of immune cells (e.g., T, B cells, NK cells), complement, or peripheral cytokines (Kiessling et al. 2017). The long-term effects of IgG depletion, particularly in the setting of additional immunosuppressive therapies, as would be expected in many MG subjects, remain uncertain.*

The Applicant has not conducted any vaccine coadministration studies with efgartigimod. section 5 (subpart 5.3; Immunization) of the proposed label states the following:

> *"Immunization with vaccines during efgartigimod (brand name: VYVGART) therapy has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are*

unknown. (b) (4)

vaccination with live or live attenuated vaccines is not recommended. (b) (4)

Summary of Pharmacokinetic Evaluation

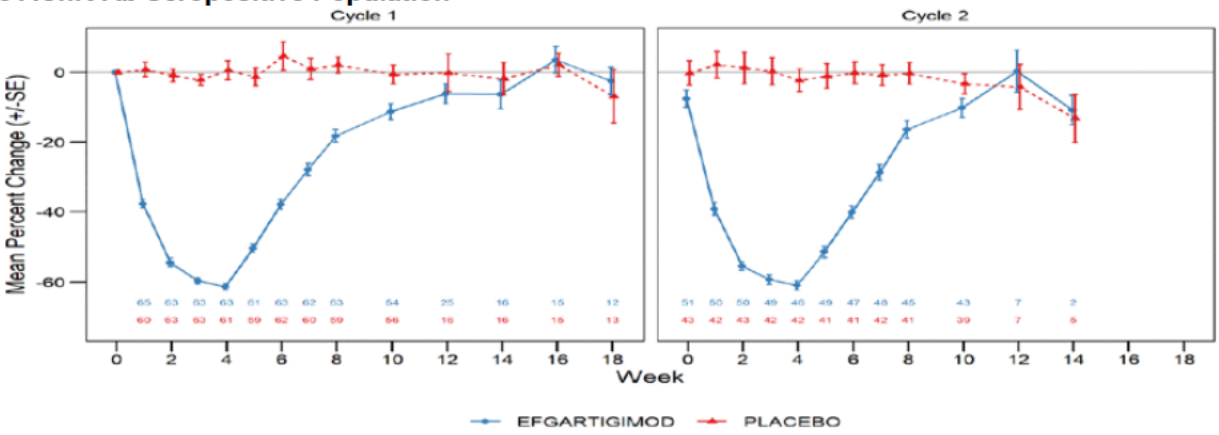
The efgartigimod elimination half-life ($t_{1/2}$) ranged from 85.1 to 104 hours (i.e., 3.5 to 4.3 days) with doses of 2.0 to 50 mg/kg. At the proposed dose of 10 mg/kg, the average $t_{1/2}$ was noted to range between 85.1 hours (i.e., approximately 3.5 days) to 117 hours (i.e., approximately 4.9 days) across the different studies. As per the Applicant, in the multiple ascending dose phase of the study no significant accumulation of efgartigimod was observed after once every 4 days dosing for 21 days and once q7d dosing for 22 days.

Summary of Pharmacodynamic Evaluation

Following a single infusion of 10 mg/kg, the respective maximal percentage reduction from baseline in total IgG (maximum effect [E_{max}]) was 55.0%. The decrease in total IgG levels reached its maximum during the first week after the last infusion of efgartigimod IV in a treatment cycle in all treatment groups. The mean E_{max} ranged from 69.4% to 77.5%. In the phase 3 study (Figure 25), total IgG returned to baseline (i.e., less than 10% reduction) by Week 12 (9 weeks after the last infusion). E_{max} was not significantly different between the tested doses or regimens, suggesting that the maximal reduction of total IgG level by efgartigimod was already achieved with the 10 mg/kg dose q7d. Similar results were obtained for the different IgG subtypes. There was no apparent difference between cycles or between AChR-Ab seropositive subjects and the overall treatment population.

Figure 25. Percent Change From Study Entry Baseline in Total IgG Levels Over Time by Cycle in the AChR-Ab Seropositive Population

APPEARS THIS WAY ON ORIGINAL



Source: Module 5.3.5.1, ARGX-113-1704, Table 14.2.8.2.1
AChR-Ab=anti-acetylcholine receptor antibody; Ig=immunoglobin; SE=standard error
Note: Cycle 3 not shown as only data for less than 10 patients (in both treatment groups) was available.
Source: Figure 4 of the clinical pharmacology summary

Reviewer's comment: (b) (4)

(b) (4)

Overview of Safety Related to IgG Depletion

As per the Applicant submitted pooled safety data sets, in Pooling Block 1 (double-blinded, placebo-controlled studies in gMG pool [Studies 1602 and 1704] using a data cutoff date of April 6, 2020 [i.e., when the pivotal Study 1704 was completed]), the most frequently (≥4% of subjects in either group) reported treatment-emergent adverse events of special interest (AESIs) by preferred term were:[11]

- Urinary tract infection (UTI) in 8 (8.3%) and 2 (2.1%) subjects in the efgartigimod and placebo groups, respectively
- Nasopharyngitis in 7 (7.3%) and 12 (12.6%) subjects in the efgartigimod and placebo groups, respectively
- Upper respiratory tract infection in 7 (7.3%) and 1 (1.1%) subjects in the efgartigimod and placebo groups, respectively
- Bronchitis in 4 (4.2%) and 1 (1.1%) subjects in the efgartigimod and placebo groups, respectively.

None of the treatment-emergent AESIs reported were serious or common terminology criteria for adverse events (CTCAE) Grade ≥3 in severity, and none led to IMP discontinuation. The only treatment-emergent AESI that resulted in IMP interruption was a UTI reported in a single subject in the efgartigimod group. No opportunistic infections were reported in subjects in the efgartigimod group. Herpes zoster and oral herpes were reported in one subject each in the efgartigimod group, and no subjects in the placebo group. Pneumonia was reported in a single subject who received efgartigimod. The treatment-emergent AESI of pneumonia was not serious or considered by the investigator to be related to IMP. The dose of efgartigimod was not changed, and the subject recovered from the event.

In Pooling Block 2 (all subjects with gMG who received efgartigimod pool), AESIs (TEAEs in the SOC Infections and Infestations) were reported in 82 (50.6%) subjects in the total efgartigimod group: 54 (56.3%) in efgartigimod group and 28 (42.4%) in placebo-efgartigimod group. The most frequently (≥4%) reported treatment-emergent AESIs by preferred term were:

- Nasopharyngitis in 22 (13.6%) subjects
- UTI in 13 (8.0%) subjects
- Upper respiratory tract infection in 12 (7.4%) subjects
- Bronchitis in 7 (4.3%) subjects

All treatment-emergent AESIs reported in the total efgartigimod group during all cycles cumulatively were of severity Grades 1 or 2 except for 10 events in 8 (4.9%) subjects, which were Grade 3. Treatment-emergent AESIs that were severity Grade 3 included COVID-19 and

[11] AESIs were not defined for Study 1602 and were defined as "Any Treatment-Emergent Adverse Event (TEAE) in the MedDRA SOC Infections and Infestations for Study 1704

influenza reported in 2 (1.2%) subjects each, and COVID-19 pneumonia, dysentery, pharyngitis, pharyngitis streptococcal, and pneumonia reported in 1 (0.6%) subject each.

Serious treatment-emergent AESIs occurred in 6 (3.7%) subjects in the total efgartigimod group during all cycles cumulatively: 5 (5.2%) subjects in the efgartigimod cohort and 1 (1.5%) subject in the placebo-efgartigimod. Serious AESIs included COVID-19 in 2 (1.2%) subjects and COVID-19 pneumonia, dysentery, pneumonia, and "pneumonia Escherichia" in 1 (0.6%) subject each. None of the serious AESIs were considered by the Investigator to be related to efgartigimod. There were no AESIs with a fatal outcome.

Reviewer's comment: *As expected, there were increased infections reported in the efgartigimod group compared to placebo group in both pools of subjects.*

Vaccination

In Studies 1704 (pivotal phase 3 study) and 1705 (open-label extension), vaccination of subjects with live or live attenuated vaccines was prohibited within 4 weeks of study entry, and vaccination with other vaccines was permitted 48 hours before or after an infusion.

Reviewer's comment: *The Applicant claims that, as per their PK and PD data, approximately 2 weeks after the last of four weekly infusions of efgartigimod IV 10 mg/kg, IgG levels begin to increase. By that time, efgartigimod concentrations dropped to <2% of the C_{max}.* (b) (4)

Reviewer Summary

(b) (4)

CBER recommends removal of the statement (b) (4)

(b) (4)

CBER also recommends modification of the following statement (b) (4)

"Immunization with vaccines during efgartigimod (brand name: VYVGART) therapy has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with any vaccine is unknown." (b) (4)

(b) (4). Vaccine utilization guidelines issued by professional medical societies and advisory committees generally recommend to healthcare providers that patients undergoing treatment with biologic immune-modulating drugs receive non-live vaccinations as indicated, preferably before starting immune-modulating therapies because, despite any potential for interference, the benefits of vaccination still likely outweigh the risks. Thus, CBER agrees that non-live vaccines should continue to be recommended in patients undergoing treatment with efgartigimod. However, we recommend that the following language be added in section 5 regarding non-live vaccinations "Immune responses elicited by non-live vaccinations received during a course of VYVGART have not been assessed."

Summary of CBER Responses to Consult Questions:

(1) Please make recommendations regarding the appropriate timing of vaccination with respect to the end of a treatment cycle with efgartigimod.

CBER Response

(b) (4). Vaccine utilization guidelines issued by professional medical societies and advisory committees generally recommend to healthcare providers that patients undergoing treatment with biologic immune-modulating drugs should not receive live vaccines. In such patients, non-live vaccinations should be administered as indicated, preferably before starting immune-modulating therapies because the benefits of vaccination still likely outweigh the risks despite any potential for interference. (b) (4) Therefore, we propose the following revisions to the Applicants proposed language:

> *"Immunization with vaccines during efgartigimod (brand name: VYVGART) therapy has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with any vaccine is unknown. Administer all age-appropriate vaccines according to immunization guidelines before initiation of treatment with VYVGART."*

(2) Please comment on the utility of checking antibody titer levels to confirm effectiveness of vaccination in subjects who received an inactivated vaccine while between treatment cycles with efgartigimod.

CBER Response

We have the following comments regarding the utility of measuring antibody responses:

(b) (4) Information regarding immune responses considered clinically meaningful by CBER for vaccine licensure are provided with the respective FDA label.

CBER recommends against use of antibody responses to non-licensed vaccines (e.g., antigens used in research only) that are of uncertain clinical significance, both generally and specifically

with regard to predicting whether immune responses to FDA-licensed vaccines will be protective.

CBER requires adequate validation of antibody assays (b) (4) based on immunogenicity data generated using those assays. In the absence of assay validation data, a rigorous assessment of the immunogenicity results generated is not feasible, thereby, significantly limiting any conclusions that can be drawn.

(3) Please comment on whether any postmarketing requirements would address outstanding questions that could help inform decision-making regarding vaccination and efgartigimod treatment.

CBER Response

We recommend that CBER requirements for the study design considerations (b) (4) be communicated to the Applicant (b) (4)

17.14. Safety Analyses by Demographic Subgroups

Table 87, Table 88, Table 89, Table 90, and Table 91 summarize the frequency of AEs by demographic subgroups in Study 1704.

A higher frequency of procedural headache was reported in subjects in the highest body mass index (BMI) quartile compared to the lowest BMI quartile. Differences in the demographic subgroups were small because of the low number of subjects in each arm (difference in subjects of no greater than three). There was a small number of subjects in treatment arms for the demographic parameters of age group, race, and region, and a conclusion regarding differences in frequency of AEs in these subgroups cannot be drawn.

Table 87 shows the frequency of common TEAEs in Study 1704 by sex. A higher frequency of UTIs was observed in females compared to males. A higher frequency of procedural headache and upper respiratory tract infection was observed in males compared to females.

Table 87. Frequency of Common TEAEs by Sex, Study 1704

	Efgartigimod		Placebo	
Preferred Term	Female (N=63) n (%)	Male (N=21) n (%)	Female (N=55) n (%)	Male (N=28) n (%)
Bronchitis	4 (6)	0	1 (2)	0
Myalgia	2 (3)	1 (5)	1 (2)	0
Procedural headache	2 (3)	2 (10)	1 (2)	0
Upper respiratory tract infection	4 (6)	3 (14)	1 (2)	0
Urinary tract infection	8 (13)	0	2 (4)	0

Source: This table was created by the reviewer using ISS Pb1 ADAE
StudyID =1704, treatment-emergent flag = yes, Group by USUBJID, dictionary-derived term, actual treatment, and demographic parameter.
Abbreviations: N, number of subjects in group; n, number of subjects with TEAE; TEAE, treatment-emergent adverse event

Table 88 shows the frequency of common TEAEs in Study 1704 by age group. Overall, the number of subjects 65 years and older in the efgartigimod arm of Study 1704 was low (less than 15). No AEs occurred in more than one subject in the 65 years and older population.

Table 88. Frequency of Common TEAEs by Age Group, Study 1704

	Efgartigimod		Placebo	
Preferred Term	18 to <65 years (N=73) n (%)	≥65 years (N=11) n (%)	18 to <65 years (N=69) n (%)	≥65 years (N=14) n (%)
Bronchitis	4 (5)	0	1 (1)	0
Myalgia	2 (3)	1 (9)	1 (1)	0
Procedural headache	4 (5)	0	1 (1)	0
Upper respiratory tract infection	7 (10)	0	1 (1)	0
Urinary tract infection	7 (10)	1 (9)	1 (1)	1 (7)

Source: This table was created by the reviewer using ISS Pb1 ADAE
StudyID =1704, treatment-emergent flag = yes, Group by USUBJID, dictionary-derived term, actual treatment and demographic parameter.
Abbreviations: N, number of subjects in group; n, number of subjects with TEAE; TEAE, treatment-emergent adverse event

Table 89 shows the frequency of common TEAEs in Study 1704 by race. The Asian race was the largest nonwhite subgroup and consisted of 16 subjects. No AEs were reported in more than one subject in the Asian race or with a difference in frequency of greater than 10% between the two races.

Table 89. Frequency of Common TEAEs by Race, Study 1704

	Efgartigimod		Placebo	
Preferred Term	Asian (N=9) n (%)	White (N=69) n (%)	Asian (N=7) n (%)	White (N=72) n (%)
Bronchitis	1 (11)	3 (4)	0	1 (1)
Myalgia	1 (11)	2 (3)	0	1 (1)
Procedural headache	0	3 (4)	0	1 (1)
Upper respiratory tract infection	0	7 (10)	0	1 (1)
Urinary tract infection	0	7 (10)	0	1 (1)

Source: This table was created by the reviewer using ISS Pb1 ADAE
StudyID =1704, treatment-emergent flag = yes, Group by USUBJID, dictionary-derived term, actual treatment and demographic parameter.
Abbreviations: N, number of subjects in group; n, number of subjects with TEAE; TEAE, treatment-emergent adverse event

Table 90 shows the frequency of common TEAEs in Study 1704 by region. Few subjects from Study 1704 were from the Japanese region (n=15). No AEs in the Japanese region were reported in more than one subject. A similar frequency of AEs was observed in the United States and the rest of the world region (difference no greater than 10%).

Table 90. Frequency of Common TEAEs by Region, Study 1704

	Efgartigimod			Placebo		
Preferred Term	Japan (N=8) n (%)	Rest of the World (N=51) n (%)	U.S. (N=25) n (%)	Japan (N=7) n (%)	Rest of the World N=61 n (%)	U.S. (N=15) n (%)
Bronchitis	1 (13)	3 (6)	0	0	1 (2)	0
Myalgia	1 (13)	1 (2)	1 (4)	0	1 (2)	0
Procedural headache	0	1 (2)	3 (12)	0	1 (2)	0
Upper respiratory tract infection	0	4 (8)	3 (12)	0	1 (2)	0
Urinary tract infection	0	5 (10)	3 (12)	0	2 (3)	0

Source: This table was created by the reviewer using ISS Pb1 ADAE
StudyID =1704, treatment-emergent flag = yes, Group by USUBJID, dictionary-derived term, actual treatment and demographic parameter.
Abbreviations: N, number of subjects in group; n, number of subjects with TEAE; TEAE, treatment-emergent adverse event; U.S., United States

The reviewer grouped subjects into BMI quartile categories in Study 1704. A higher frequency of procedural headache was reported in subjects in the highest BMI quartile compared to the lowest BMI quartile. Table 91 shows the frequency of common TEAEs in Study 1704 in subjects in the highest and lowest BMI quartile categories.

Table 91. Common TEAEs in the Highest and Lowest BMI (kg/m^2) Quartile Categories, Study 1704

	Efgartigimod		Placebo	
Preferred Term	≤23.1 (N=22) n (%)	>32.1 (N=21) n (%)	≤23.1 (N=20) n (%)	>32.1 (N=20) n (%)
Bronchitis	0	1 (5)	0	0
Myalgia	1 (5)	1 (5)	0	0
Procedural headache	0	2 (10)	0	0
Upper respiratory tract infection	1 (5)	2 (10)	0	0
Urinary tract infection	3 (14)	1 (5)	0	2 (10)

Source: This table was created by the reviewer using ISS Pb1 ADAE
StudyID =1704, treatment-emergent flag = yes, Group by USUBJID, dictionary-derived term, actual treatment and demographic parameter.
Abbreviations: BMI, body mass index; N, number of subjects in group; n, number of subjects with TEAE; TEAE, treatment-emergent adverse event

17.15. Human Carcinogenicity or Tumor Development

Overall, the reviewer did not find the database to be sufficient in assessing the carcinogenicity of efgartigimod because of the small number of subjects in Studies 1704, 1602, and 1705 (n=162) and the short mean duration of exposure to efgartigimod (369 days for subjects receiving at least 1 cycle of efgartigimod).

The same frequency of TEAEs within the SOC of Neoplasm was observed in the efgartigimod and placebo arms of Study 1704 (1%). The preferred term of rectal adenocarcinoma was reported in one efgartigimod-treated subject.

No TEAEs within the SOC of Neoplasm were observed in pooled Studies 1704 and 1602.

In pooled Studies 1704, 1602, and 1705 after the 90-Day Safety Update, TEAEs within the SOC of Neoplasm were reported in seven subjects (4%). Preferred terms included squamous cell carcinoma (n=2), adenocarcinoma of colon, oropharyngeal squamous cell carcinoma, pancreatic

carcinoma, rectal adenocarcinoma, lung neoplasm malignant, neoplasm malignant, prostate cancer, and squamous cell carcinoma of the vulva.

Refer to the Section 17.3.2 for a review of SAEs related to neoplasm.

17.16. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

The reviewer did not identify any adverse events of overdose in Studies 1704, 1602, and 1705 in a search of AEs using overdose as the preferred term, high-level term, or high-level group term.

The Applicant reviewed the clinical program for cases of overdose which were defined as a subject receiving >10% of the amount planned in the protocol.

Seven subjects received doses >10% of the amount planned in the protocol. In the 90-Day Safety Update, the Applicant had noted eight subjects whose doses were >10% of the amount planned in the protocol. However, in an information response, dated August 12, 2021, to an information request dated August 9, 2021, the Applicant noted that one of the subjects was not considered an overdose because of an update to the actual dose the subject had received (Subject (b) (6)).

Of the seven subjects who received doses >10% of the amount planned in the protocol, AEs were not reported within a year of the overdose in three subjects. In the remaining four subjects, the following preferred terms were reported within a month of the overdose: b-lymphocyte count decreased (n=2), t-lymphocyte count decreased (n=2), blood thyroid stimulating hormone increased, nasopharyngitis, asthenia, myalgia, urinary tract infection, myasthenia gravis, balance disorder, facial paresis, rash, and restless legs syndrome. B- and t-lymphocyte count decreased were reported twice in the same subject. Overdoses ranged between 10 to 20% higher than the planned dose by protocol. One of the AEs was serious, occurring in a subject who was hospitalized for myasthenia gravis and had received 10% more of a dose planned by protocol (Subject (b) (6)). The case is discussed further in Section 17.3.2.

Overall, the reviewer did not identify a role for efgartigimod in the AEs reported in the overdoses because of the unique preferred terms reported in the cases.

Abuse Potential

The reviewer did not identify a safety signal for abuse potential in a search of TEAEs related to abuse potential.

The reviewer searched for TEAEs using the following preferred terms: abnormal dreams, acute psychosis, aggression, apathy, confusional state, depersonalization/derealization disorder, disorientation, dizziness, drug tolerance, drug withdrawal syndrome, dysphoria, euphoric mood, feeling abnormal, feeling drunk, feeling of relaxation, hallucination, hallucination visual, hallucination auditory, illusion, inappropriate affect, mood swings, overdose, seizure, somnolence, and thinking abnormal.

In Study 1704, the frequency of dizziness in the efgartigimod arm did not exceed placebo (4% versus 6%, respectively). Similar findings were observed in pooled Studies 1704 and 1602. In

pooled Studies 1704, 1602, and 1705, dizziness was reported in 6% of subjects. In pooled Studies 1704, 1602, and 1705, somnolence was reported in two subjects (1%). No other TEAEs related to abuse potential in efgartigimod-treated subjects in Studies 1704, 1602, or 1705 were identified.

Withdrawal and Rebound

The reviewer did not identify any AEs belonging to the MedDRA Drug Withdrawal Standardised MedDRA Query in a search of TEAEs in Studies 1704, 1602, and 1705.

The Applicant notes that no studies or systematic analyses to evaluate potential withdrawal and rebound effects of efgartigimod have been conducted.

17.17. Suicide-Related Events

Overall, the reviewer did not find the database to be sufficient in assessing the suicidality of efgartigimod because of the low number of subjects in Studies 1704, 1602, and 1705 (n=162).

Suicidal assessments were made by asking subjects the following question from the Patient Health Questionnaire item 9, “Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?” The following responses were possible: “not at all,” “several days,” “more than half the days,” or “nearly every day.”

In Study 1602, all subjects reported postbaseline responses of “not at all.”

In Study 1704, all subjects except for four reported postbaseline responses of “not at all.” In the remaining four subjects, one subject in the efgartigimod arm and three on placebo reported “several days” (1% versus 4%, respectively).

At the October cut-off date for Study 1705, all but six subjects reported postbaseline responses of “not at all.” Five subjects reported “several days” (4%), and one subject reported “more than half the days” (1%).

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations)

As further described in the Clinical Inspection Summary report from the Office of Scientific Investigations, the clinical sites of Drs. Karam, Peric, and Szczechowski were inspected in support of this BLA and covered Protocol ARGX-113-1704. Despite some protocol deviations noted at the sites of Drs. Karam and Peric, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the indication.

Inspections did not identify any data discrepancies between source and Applicant data line listings for primary efficacy data (MG-ADL scores) but did identify discrepancies for key secondary efficacy data (QMG scores) at the sites of Drs. Karam and Peric. Specifically, QMG individual items for some subjects were incorrectly scored at these sites which affected the calculation of QMG total scores. The incorrect scores were not identified by the Applicant such that the Applicant data line listings include these errors, as discussed further below.

20.1. QMG Quality Control

Site inspections found discrepancies in total QMG scores that were caused by sites incorrectly assigning the severity scores to individual test items of the QMG. An information request was sent to the Applicant on September 13, 2021, asking the Applicant to perform quality control on the submitted QMG data for the pivotal Study 1704 and to submit corrected datasets.

The Applicant reviewed a total of 39331 of the 39825 QMG records (98.8% of the total QMG records) from 165 subjects (98.8% of subjects who participated in Study 1704). The JPN00002 site, which recruited two subjects, was not able to accommodate the review in time due to administrative reasons. In total 259 (0.65%) QMG items were updated, 112 (0.55%) in efgartigimod-treated subjects and 147 (0.75%) in placebo-treated subjects. This change had minimal effect on the efficacy analysis.

20.2. Grade F Spirometry

Site inspections found that spirometry reports for some subjects in Study 1704 had “Quality Control Grade F” (no acceptable tests). An information request was sent to the Applicant on July 28, 2021, to clarify how Grade F spirometry affected the forced vital capacity (FVC) values used to calculate the QMG score.

Spirometry produces a %FVC (an FVC expressed as a percentage of the predicted FVC) regardless of the quality assessment and the %FVC, per protocol, is transformed into a score by the investigator where %FVC ≥80 yields score 0, %FVC 65 to 79 yields score 1, %FVC 50 to 64 yields score 2, and %FVC <50 yields score 3. The spirometry grading system is based primarily on the reproducibility of acceptable tests. Grade F spirometry % outcome is machine-generated and is dependent on the patient’s compliance with following spirometry instructions. Anecdotal reports have suggested that a quarter of spirometry tests may yield a grade F measurement, varying by individual lab (Johnston 2018). The Applicant reported that of 3077 spirometry measurements for Study 1704, 1203 (39%) grade F measurements were documented.

Table 92. QMG Scores, Frequency of Grade F Quality for Vital Capacity (Item 8)

	All Data in Any Cycle [1]	
Spirometry Quality Grading F	**Efgartigimod (N=1566)**	**Placebo (N=1511)**
No, n (%)	885 (56.5)	797(52.7)
Yes, n (%)	600 (38.3)	603(39.9)
Missing, n (%)	81 (5.2)	111(7.3)

Source: Table 2 of Response to FDA Request for information request received September 13, 2021
Abbreviations: N, number of subjects in group; n, number of subjects with Spirometry Quality Grade F; QMG, Quantitative Myasthenia Gravis

To evaluate the impact of Grade F quality on the QMG responder assessment, the Applicant performed a sensitivity analysis that imputed the worst score (3-severe) for QMG Item 8, whenever the spirometry quality was assessed to be Grade F.

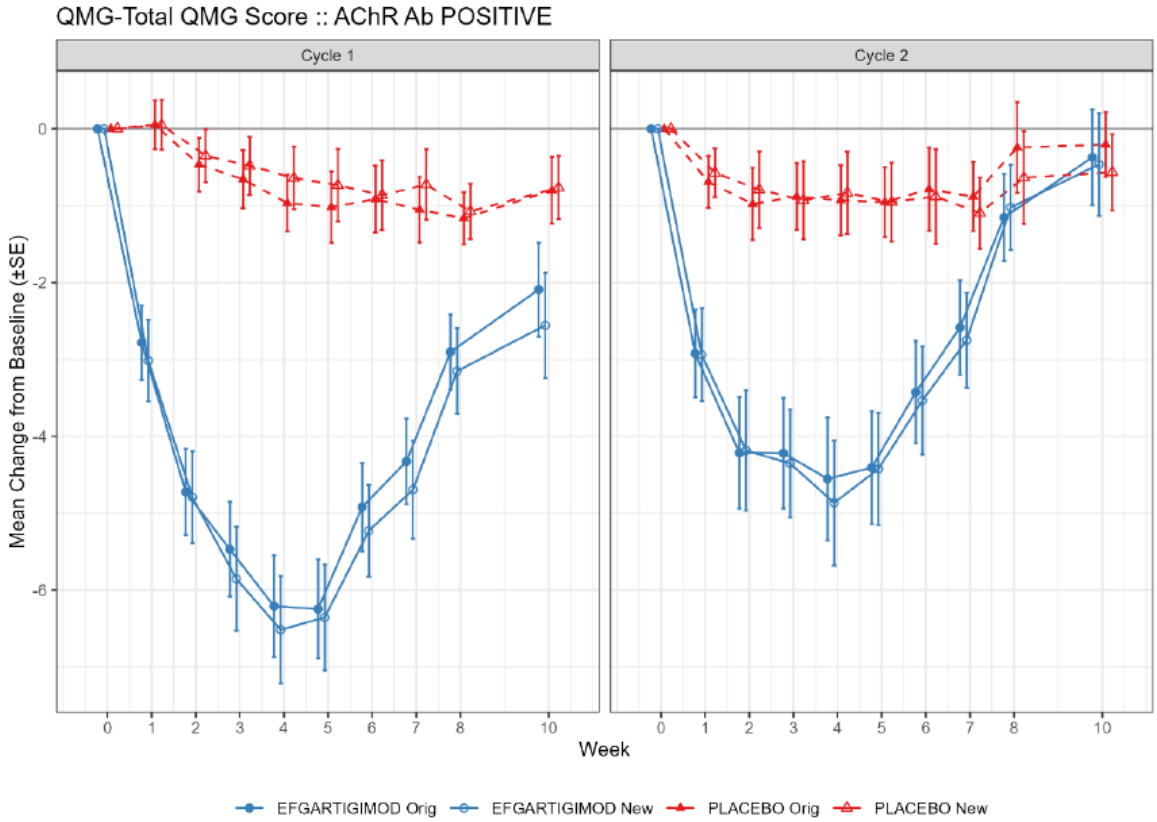
This analysis was performed on the subset of AChR-Ab seropositive subjects for which the quality grading was available in the first 8 weeks of Cycle 1, where QMG response was assessed.

Two types of changes were applied to the initially submitted analysis dataset (ADQS1):

(1) Correction of incorrectly scored individual QMG items as mentioned in Section 20.1 "QMG Quality Control"
(2) Spirometry measurements of the subject's FVC (QMG questionnaire item 8) that were either missing or assigned a grade F in the quality assessment were imputed with the worst score

Figure 26 shows the mean change in QMG from cycle baseline before and after the corrections from this quality review.

Figure 26. Mean Change in QMG From Cycle Baseline (Seropositive Population) in the Original Submission Data Compared to the Corrected Data from Quality Control



Source: Response to Information Request received October 1, 2021
Abbreviations: AChR Ab, acetylcholine receptor-ant body; QMG, Quantitative Myasthenia Gravis; SE, standard error

The Applicant reported the results of the sensitivity analysis, shown in Table 93.

Table 93. QMG Responders in the AChR-Ab Seropositive Population During Cycle 1, mITT Analysis Set, Updated

QMG Responders	Efgartigimod (N=63)	Placebo (N=64)	Efgartigimod vs. Placebo	
			Odds Ratio (95% CI)	P-value
n (%)	39 (61.9)	6 (9.4)	15.795 (5.372, 55.100)	<0.0001

Source: Response to information request dated October 1, 2021
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in group; n, number of responders; QMG, Quantitative Myasthenia Gravis

However, in the Applicant's analysis, subjects whose data the Applicant could not conduct a QC check for were excluded for the analysis. Additionally, a worst-case type of analysis for the purpose of efficacy evaluation should only impute the worst score for the postbaseline QMG Item 8 values for the efgartigimod group. The reviewer conducted an analysis that includes all subjects in the modified intent-to-treat analysis set and imputes the worst score only for the postbaseline QMG Item 8 values for the efgartigimod group. The result remained statistically significant for this key secondary endpoint. (Table 94). The result of QMG is very robust as the statistical significance will maintain unless the number of responders in efgartigimod group is reduced to less than 20 based on the reviewer's analysis (not shown in table).

Table 94. Worst Case Analysis of QMG Responders in the AChR-Ab Seropositive Population During Cycle 1, mITT Analysis Set

QMG Responders	Efgartigimod (N=65)	Placebo (N=64)	Efgartigimod vs. Placebo	
			Odds Ratio (95% CI)	P-value
n (%)	38 (58.5)	9 (14.1)	8.52 (3.35, 23.84)	<0.0001

Source: FDA reviewer.
Abbreviations: AChR-Ab, acetylcholine receptor-antibody; CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in group; n, number of responders; QMG, Quantitative Myasthenia Gravis

21. Labeling Summary of Considerations and Key Additional Information

Significant modifications to the Applicant proposed Prescribing Information (PI) submitted on March 12, 2021, are described in Table 95. The Highlights and Table of Contents were revised to reflect edits to the Full Prescribing Information.

Table 95. Summary of Significant Modifications to the Full Prescribing Information

Section	Applicant's Proposal	Modification/Rationale
Indications and Usage (1)	Application proposed text for the section: VYVGART is indicated for the treatment of adult patients with generalized Myasthenia Gravis (gMG).	The Division of Neurology 1 (DN1) does not agree with an indication for the entire gMG population (acetylcholine receptor positive [AChR+] and acetylcholine receptor negative [AChR-]. The decision is based, in summary, because for the primary endpoint of the MG-ADL responders, the AChR+ population was the prespecified analysis. Although the overall population (AChR+ and AChR-) was a prespecified secondary endpoint, the positive results for this analysis was driven by the AChR+ population. (b) (4) . Please see the clinical and statistical reviews for further information. The revised Indications and Usage statement is as follows: VYVGART is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Section	Applicant's Proposal	Modification/Rationale
Dosage and Administration (2)	Vaccination recommendations were not proposed for inclusion in section 2.	DN1 added subsection "2.1 Recommended Vaccination Prior to Treatment". This subsection was added to identify this specific safety procedure that should be implemented before initiating therapy with VYVGART. DN1 included this information as 2.1 since lack of knowledge of the information or nonadherence to the recommendation could have serious consequences for the patient. See the Guidance for Industry, Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, March 2010. For further information regarding revisions to vaccination recommendations, see Warnings and Precautions below.
	The Applicant proposed a general statement regarding the duration between treatment cycles: (b) (4)	The earliest possible time to a subsequent treatment cycle was 50 days after the initial infusion (median time 10 weeks; range 8 to 26 weeks) in Study 1, and 7 weeks in the open-label extension study. Therefore, DN1 revised the proposed sentences (revision shown below) to note the lack of safety data with respect to initiation of subsequent treatment cycles at any earlier timeframe: The safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.
		DN1, in consultation with the Division of Medication Error Prevention and Analysis, revised the layout of the Preparation and Administration subsection to improve clarity. In addition, information that is not necessary to relay to a healthcare provider was deleted.

Section	Applicant's Proposal	Modification/Rationale
Warnings and Precautions (5)	Applicant proposed subsection: **5.1 Infections** (b) (4) , the risk of infections may increase. The most common infections observed (b) (4) were upper respiratory tract infections *[see Adverse Reactions (6.1)]*. Monitor for clinical signs and symptoms of infections (b) (4)	DN1 added urinary tract infections as a most common infection with VYVGART treatment. DN1 also included the rate of infections and rate of below normal white blood cell counts compared to placebo, per recommendations in the Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format, October 2011. Also, current labeling recommendations are to avoid ambiguous and uninformative statements (b) (4) therefore, the management strategies were also revised as follows: Delay VYVGART administration in patients with an active infection until the infection is resolved. During treatment with VYVGART, monitor for clinical signs and symptoms of infections. If serious infection occurs, administer appropriate treatment and consider withholding VYVGART until the infection has resolved.

Section	Applicant's Proposal	Modification/Rationale
	Applicant proposed subsection: (b) (4)	DN1 revised the term (in subsection title and text) (b) (4) to "hypersensitivity reactions" to better describe the reactions observed in the clinical trials. DN1 also included the specific types of reactions observed and time to onset, per the recommendations in the Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products, August 2014. The management recommendations were revised (b) (4) The revised subsection text is as follows: **5.2 Hypersensitivity Reactions** Hypersensitivity reactions, including rash, angioedema, and dyspnea, were observed in VYVGART-treated patients. In clinical trials, hypersensitivity reactions were mild or moderate, occurred within one hour to three weeks of administration, and did not lead to treatment discontinuation. Monitor patients during administration and for 1 hour thereafter for clinical signs and symptoms of hypersensitivity reactions *[see Dosage and Administration (2.3)]*. If a hypersensitivity reaction occurs during administration, discontinue VYVGART infusion and institute appropriate supportive measures if needed.
	The Applicant proposed subsection (b) (4)	DN1, in consultation with CBER Division of Vaccines Research Review, removed (b) (4)

Section	Applicant's Proposal	Modification/Rationale
Adverse Reactions (6)	The Applicant proposed the following to be included in the common adverse reaction table (%VYVGART/% placebo): (b) (4) respiratory tract infection (b) (4) urinary tract infection (b) (4) (b) (4) myalgia (b) (4) (b) (4) headache (b) (4)	To show an accurate presentation of the common adverse reaction, like terms were combined, and the rates were revised accordingly. DN1 added paresthesia to the common adverse reaction table. See below for grouped terms and rates (%VYVGART/% placebo): respiratory tract infection (33/29): includes respiratory tract infection, bronchitis, pharyngitis, pneumonia, sinusitis, upper respiratory tract infection, viral pharyngitis, viral tracheitis, chronic sinusitis, influenza, and nasopharyngitis Headache (32/29): includes migraine and procedural headache. Urinary tract infection (10/5) Paresthesia (7/5): includes oral hypoesthesia, hypoesthesia, hyperesthesia Myalgia (6/1)
Drug Interactions (7)	The Applicant proposed text for the section: (b) (4)	The initial sentence was moved to subsection 12.3 since it does not provide any clinically significant drug interaction information. DN1, the Office of Clinical Pharmacology, and the Office of Infectious Diseases/Division of Antivirals discussed and collaborated to reach labeling language that takes into account both short-term and chronic use of medications that bind to FcRn and that there are alternate treatments available for gMG. The following is agreed upon text: Concomitant use of VYVGART with medications that bind to 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. Closely monitor for reduced effectiveness of medications that bind to the human neonatal Fc receptor. When concomitant long-term use of such medications is essential for patient care, consider discontinuing VYVGART and using alternative therapies.
Use in Specific Populations (8)	The Applicant proposed the following sentence in 8.1 Pregnancy: Treatment of pregnant women with VYVGART should only be considered if the clinical benefit outweighs the risks.	As this proposed sentence is from CFR 201.80, which applies to labeling that is not required to be in Physician Labeling Rule (PLR) format, the Division deleted the sentence.

Section	Applicant's Proposal	Modification/Rationale
Clinical Pharmacology (12)	The Applicant proposed text for the subsection: (b) (4)	The Division of Pharmacology/Toxicology for Neuroscience (DPT-N) and DN1 revised the labeling text to only include what is known and relevant about the mechanism of action for the indication of gMG and to remove (b) (4) (see the Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, December 2016). The revised subsection text is as follows: Efgartigimod alfa-fcab is a human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG.
	In 12.2 Pharmacodynamics, the Applicant proposed to include the (b) (4)	DN revised the text to simplify the language and remove redundant information. (b) (4)
	In 12.3 Pharmacokinetics, the Applicant proposed to include (b) (4)	DN1 deleted this proposed (b) (4) Additional edits were made based on the Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products —Content and Format, December 2016.
Nonclinical Toxicology (13)	13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility	There was general agreement about the conclusions with respect to the animal studies. Under the Impairment of Fertility heading, DPT-N proposed to include the safety margins with respect to recommended human dose.

Section	Applicant's Proposal	Modification/Rationale
	In 13.2 Animal Toxicology, the applicant proposed the following labeling text: (b) (4)	This subsection was removed since there were no significant findings in these animal studies that are necessary for the safe and effective use of VYVGART in humans [see CFR 201.57(c)(14)(ii)].
Clinical Studies (14)	The Applicant proposed to include (b) (4)	DN1 removed (b) (4) see discussion under Indications and Usage for additional information.
	The Applicant proposed (b) (4)	This proposed inclusion was not acceptable, but DN1 and the Office of Biostatistics/Division of Biometrics 1 (DB1) agreed to a graphic depicting the response over time with the full range of responses, including worsening.
	The Applicant proposed to include (b) (4)	DN1 and DB1 did not agree to the inclusion as this was an exploratory endpoint.

22. Postmarketing Requirements and Commitments

The following postmarketing requirement (PMR) will be issued at the time of approval.

PMR #4202-1: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Vyvgart (efgartigimod) 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.

PMR Milestones:

Draft Protocol Submission	03/2022
Final Protocol Submission:	01/2023
Interim /Other[12]:	03/2024

[12] Interim or "other" milestones may include interim report submission or subject accrual milestones. Justification for these milestones should be described in Section D.3,

	03/2025
	03/2026
	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
Study/Trial Completion:	01/2033
Final Report Submission:	12/2033

23. Financial Disclosure

Table 96. Covered Clinical Studies: Study 1704

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 126		
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): 1		
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: 1: (b) (6) 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)

24. References

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Guidance for Industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019)

Guidance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011)

25. Review Team

Table 97. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Michael Matthews
Nonclinical Reviewers	Barbara Wilcox Melissa Banks-Muckenfuss
Nonclinical Team Leader	Lois Freed
Office of Clinical Pharmacology Reviewer(s)	Gopichand Gottipati Jie Liu Hobart Rogers
Office of Clinical Pharmacology Team Leader(s)	Bilal AbuAsal Sreedharan Sabarinath Atul Bhattaram Christian Grimstein
Clinical Reviewer	Rainer Paine
Clinical Team Leader	Laura Jawidzik
Clinical Analyst	Rui Li
Clinical Data Scientist	Ling Cao
Clinical Data Scientist TL	Jin (Jinzhong) Liu
Statistical Reviewer	Xiang Ling
Statistical Team Leader	Kun Jin
Labeling (ADL)	Tracy Peters
Safety Reviewer	Natalie Branagan
Safety Reviewer TL	Sally Jo Yasuda
Cross-Disciplinary Team Leader	Laura Jawidzik
Division Director (pharm/tox)	Lois Freed
Division Director (OCP)	Issam Zineh
Division Director (OB)	Jim Hung
Division Director (clinical)	Teresa Buracchio
Office Director (or designated signatory authority)	Billy Dunn

Abbreviations: ADL, Associate Director for Labeling; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; TL, team leader

Table 98. Additional Reviewers of Application

Office or Discipline	Name(s)
OBP RBPM	Kristine Leahy
OBP Reviewer	Sang Bong Lee
OBP Team Lead	Chana Fuchs
OPMA facility/micro branch chief	Thuy Thanh Nguyen
OPMA facility team leader	Zhong Li
OPMA micro team leader for DS/DP	Max Van Tassell
OPMA primary DS micro/facility	Wendy Tan
OPMA primary DP micro/facility	Wayne Seifert
OSI	Cara Alfaro
OSI Team Lead	Phillip Kronstein
OSE RPM	Casmir Ogbonna
OSE/DEPI	
OSE/DMEPA	Beverly Weitzman
OSE/DMEPA TL	Celeste Karpow
OSE/DRISK	Carlisha Gentles
OPDP	Sapna Shah
CBER Vaccine consult	Soumya Chatterjee

Abbreviations: CBER, Center for Biologic Evaluation and Research; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OBP, Office of Biotechnology Products; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing and Assessment; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; RPM, regulatory project manager; TL, team lead

Table 99. Signatures of Reviewers

See attached pages.

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Teresa Buracchio, MD	OND/DN1	Enter sections. ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Teresa Buracchio -S Digitally signed by Teresa Buracchio -S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0 9 2342 19200300 100 1 1=2001365871, cn=Teresa Buracchio -S Date: 2021 12 14 15:43:16 05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Laura Jawidzik, MD	OND/DN1	Sections 1 and 2 ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Laura A. Jawidzik -S Digitally signed by Laura A. Jawidzik -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001862682, cn=Laura A. Jawidzik -S Date: 2021.12.08 12:32:47 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Rainer Paine, MD, PhD	OND/DN1	Section 1, 2, 3, 4, 6, 15, 16 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Eric Bastings, MD	OND/ON	Enter sections. ☐ Authored ☐ Contributed ☒ Approved
Office Deputy Director	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Teresa Buracchio, MD	OND/DN1	Enter sections. ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Laura Jawidzik, MD	OND/DN1	Sections 1 and 2 ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Rainer Paine, MD, PhD	OND/DN1	Section 1, 2, 3, 4, 6, 15, 16 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Rainer W. Paine -S Digitally signed by Rainer W. Paine -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000529540, cn=Rainer W. Paine -S Date: 2021.12.07 16:34:15 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sally Jo Yasuda, MS, PharmD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Sally U. Yasuda -S Digitally signed by Sally U Yasuda -S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300193521, cn=Sally U Yasuda -S Date: 2021.12.14 10:25:16 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Natalie Branagan, MD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tracy Peters, PharmD	OND/DN1	Section 21 ☐ Authored ☒ Contributed ☐ Approved
Associate Director for Labeling	**Signature:** Tracy Peters -S Digitally signed by Tracy Peters -S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, cn=Tracy Peters -S, 0.9.2342.19200300.100.1.1=2000625319 Date: 2021.12.14 08:57:31 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiang Ling, PhD	OB/DBI	Sections 6, 15, 16, 20 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sally Jo Yasuda, MS, PharmD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Natalie Branagan, MD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Natalie M. Branagan -S Digitally signed by Natalie M Branagan S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2002412619 cn Natalie M Branagan S Date: 2021 12 08 08:07:37 05 00		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tracy Peters, PharmD	OND/DN1	Section 21 ☐ Authored ☒ Contributed ☐ Approved
Associate Director for Labeling	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiang Ling, PhD	OB/DBI	Sections 6, 15, 16, 20 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sally Jo Yasuda, MS, PharmD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Natalie Branagan, MD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tracy Peters, PharmD	OND/DN1	Section 21 ☐ Authored ☒ Contributed ☐ Approved
Associate Director for Labeling	**Signature:** Tracy Peters -S Digital y signed by Tracy Peters S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Tracy Peters S 0 9 2342 19200300 100 1 1=2000625319 Date: 2021 12 14 08 57:31 05 00		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiang Ling, PhD	OB/DBI	Sections 6, 15, 16, 20 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sally Jo Yasuda, MS, PharmD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Natalie Branagan, MD	OND/DN1	Sections 1, 2, 3, 4, 7, 8, 17, 22 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tracy Peters, PharmD	OND/DN1	Section 21 ☐ Authored ☒ Contributed ☐ Approved
Associate Director for Labeling	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiang Ling, PhD	OB/DBI	Sections 6, 15, 16, 20 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Xiang Ling -S Digitally signed by Xiang Ling -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiang Ling -S, 0.9.2342.19200300.100.1.1=2000343063 Date: 2021.12.07 15:08:19 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Kun Jin, PhD	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Kun Jin -S Digitally signed by Kun Jin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kun Jin -S, 0.9.2342.19200300.100.1.1=1300105908 Date: 2021.12.14 11:11:00 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Barbara Wilcox, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lois Freed, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Lois M. Freed -S Digitally signed by Lois M Freed S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Lois M Freed S 0 9 2342 19200300 100 1 1=1300076414 Date: 2021 12 14 10:18:26 05 00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Gopichand Gottipati, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Kun Jin, PhD	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Barbara Wilcox, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Barbara J. Wilcox -S Digitally signed by Barbara J. Wilcox -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085067, cn=Barbara J. Wilcox -S Date: 2021.12.09 14:22:05 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lois Freed, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Gopichand Gottipati, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Kun Jin, PhD	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Barbara Wilcox, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lois Freed, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Lois M. Freed -S Digitally signed by Lois M Freed -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Lois M Freed -S 0 9 2342 19200300 100 1 1=1 300076414 Date: 2021 12 14 10:18:26 05 00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Gopichand Gottipati, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Kun Jin, PhD	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Barbara Wilcox, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lois Freed, PhD	OND/DPT-N	Sections 5, 13, 14, 18 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Gopichand Gottipati, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Gopichand Gottipati -S Digitally signed by Gopichand Gottipati -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002119040, cn=Gopichand Gottipati -S Date: 2021.12.08 10:37:33 -05'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Bilal AbuAsal, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Bilal Abu Asal -S Digitally signed by Bilal Abu Asal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bilal Abu Asal -S, 0.9.2342.19200300.100.1.1=2001244679 Date: 2021.12.14 14:09:08 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jie Liu, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Immunogenicity	Frederick Mills, PhD	OBP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:**		

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Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Bilal AbuAsal, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jie Liu, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Jie Liu -S Digitally signed by Jie Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jie Liu -S, 0.9.2342.19200300.100.1.1=2002995351 Date: 2021.12.07 16:10:48 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Immunogenicity	Frederick Mills, PhD	OBP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:**		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Bilal AbuAsal, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jie Liu, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Venkatesh A. Bhattaram -S Digitally signed by Venkatesh A. Bhattaram -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300212823, cn=Venkatesh A. Bhattaram -S Date: 2021.12.14 09:04:32 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Immunogenicity	Frederick Mills, PhD	OBP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:**		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Bilal AbuAsal, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jie Liu, PhD	OCP	Sections 5, 6, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, PhD	OCP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Immunogenicity	Frederick Mills, PhD	OBP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Reviewer	**Signature:** Frederick C. Mills -S Digitally signed by Frederick C. Mills -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Frederick C. Mills -S Date: 2021.12.07 15:27:56 -05'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Immunogenicity	Gerry Feldman, PhD	OBP	Sections 5, 6, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Gerald M. Feldman -S Digitally signed by Gerald M. Feldman -S Date: 2021.12.07 14:47:12 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Michael Matthews	OND/ORO/N1	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Michael Matthews -S Digitally signed by Michael Matthews -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013761104, cn=Michael Matthews -S Date: 2021.12.07 11:40:48 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Heather Bullock, RN, BSN, MSHS	OND/ORO/N1	Section 12 ☐ Authored ☐ Contributed ☒ Approved
Supervisor	**Signature:** Heather M. Bullock -S4 Digitally signed by Heather M Bullock S4 DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2000463628 cn=Heather M Bullock S4 Date: 2021 12 07 14:28:26 05'00'		

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/s/

TERESA J BURACCHIO on behalf of LAURA A JAWIDZIK
12/17/2021 01:39:38 PM

TERESA J BURACCHIO
12/17/2021 01:39:56 PM

WILLIAM H Dunn
12/17/2021 02:38:01 PM