

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761286Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Table 2: Application information													
Application type	BLA												
Application number(s)	761286												
Priority or standard	Priority												
Submit date(s)	10/24/2022												
Received date(s)	10/24/2022												
PDUFA goal date	6/24/2023												
Division/office	Division of Neurology I (DNI)												
Review completion date	6/23/2023												
Established/proper name	rozanolixizumab-noli												
(Proposed) proprietary name	Rystiggo												
Pharmacologic class	Neonatal FcRn blocker												
Other product name(s)	Also referred to as UCB7665												
Applicant	UCB, Inc												
Dosage form(s)/formulation(s)	Solution for injection. Each 2 mL single-dose vial contains 280 mg of rozanolixizumab-noli, histidine (2.10 mg), L-histidine hydrochloride monohydrate (9.74 mg), proline (57.56 mg), polysorbate 80 (0.60 mg), and water for injection, USP with a pH of 5.6.												
Dosing regimen	The recommended dosage is administered as a subcutaneous infusion once weekly for 6 weeks. <table><tr><th>Body Weight of Patient</th><th>Dose</th><th>Volume to be Infused</th></tr><tr><td>Less than 50 kg</td><td>420 mg</td><td>3 mL</td></tr><tr><td>50 kg to less than 100 kg</td><td>560 mg</td><td>4 mL</td></tr><tr><td>100 kg and above</td><td>840 mg</td><td>6 mL</td></tr></table>	Body Weight of Patient	Dose	Volume to be Infused	Less than 50 kg	420 mg	3 mL	50 kg to less than 100 kg	560 mg	4 mL	100 kg and above	840 mg	6 mL
Body Weight of Patient	Dose	Volume to be Infused											
Less than 50 kg	420 mg	3 mL											
50 kg to less than 100 kg	560 mg	4 mL											
100 kg and above	840 mg	6 mL											
Applicant-proposed indication(s)/population(s)	Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody positive												
SNOMED CT code for proposed indication disease term(s) ¹	91637004 Myasthenia Gravis												
Regulatory action	Approval												
Approved dosage (if applicable)	As above												
Approved indication(s)/population(s) (if applicable)	For the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody positive												
SNOMED CT code for approved indication disease term(s) ¹	91637004 Myasthenia Gravis												

¹ For internal tracking purposes only.

Abbreviations: AChR, acetylcholine receptor; BLA, biologics license application; DNI, Division of Neurology I; FcRn, neonatal fragment crystallizable receptor; MuSK, muscle-specific kinase; UCB, Union Chimique Belge; USP, United States Pharmacopeia

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BLA 761286

Rystiggo (rozanolixizumab)

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Glossary

AChE	acetylcholine esterase
AChR	acetylcholine receptor
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
BUN	blood urea nitrogen
CD	cluster of differentiation
CDER	Center for Drug Evaluation and Research
CL	clearance
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease of 2019
CSF	cerebrospinal fluid
CSR	clinical study report
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
E _{max}	maximum effect
F	fraction absorbed
Fc	fragment crystallizable
FcRn	neonatal fragment crystallizable receptor
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GD	gestational day
GI	gastrointestinal
gMG	generalized myasthenia gravis
HD	high density
HDF	hemodiafiltration
HDL	high-density lipoprotein
HUVEC	human umbilical vein endothelial cells
ICE	intercurrent event
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
IGRA	interferon gamma release
IIV	interindividual variability
IND	investigational new drug
IR	information request
ITP	immune thrombocytopenia
IV	intravenous
IVIg	intravenous immunoglobulin
K _{out}	first-order elimination rate constant

KLH	keyhole limpet hemocyanin
LD	lactational day
LDF	laser Doppler flowmetry
LDL	low-density lipoprotein
LFT	liver function test
LLOQ	lower limit of quantification
LS	least squares
MAT	mean absorption time
MG	myasthenia gravis
MG-ADL	myasthenia gravis activities of daily living
MG-C	myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
MGSPRO	myasthenia gravis symptoms PRO
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
MuSK	muscle-specific kinase
NAb	neutralizing antibodies
NMJ	neuromuscular junction
OLE	open-label extension
PCR	polymerase chain reaction
PD	pharmacodynamic
PEX	plasma exchange
PGI-S	patient global impression of severity scale
PI	Prescribing Information
PK	pharmacokinetic
PND	postnatal day
PopPK	population pharmacokinetics
PRO	patient-reported outcome
PT	prothrombin time
QMG	quantitative myasthenia gravis
SAE	serious adverse event
SARS-CoV2	severe acute respiratory syndrome 2
SC	subcutaneous
SOC	system organ class
TB	tuberculosis
TEAE	treatment-emergent adverse event
TK	toxicokinetics
TMDD	target-mediated drug disposition
UCB	Union Chimique Belge
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

Union Chimique Belge (UCB) submitted a biologics license application (BLA) 761286 for rozanolixizumab. Rozanolixizumab is a neonatal fragment crystallizable receptor (FcRn) blocker for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody positive.

BLA 761286 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 MG0003), with confirmatory evidence from pharmacodynamic/mechanistic data and knowledge of other drugs in class, that provide substantial evidence of effectiveness of rozanolixizumab for the indication and supports approval for the treatment of adults with gMG who are anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody positive. Study MG0003 was a double-blind, placebo-controlled, multicenter study that provided reliable and highly statistically significant ($p < 0.001$) evidence of an important patient-reported impact and clinical benefit on daily function on an acceptable primary outcome (i.e., change from baseline to day 43 on the Myasthenia Gravis-Specific Activities of Daily Living [MG-ADL]). Efficacy was further supported by a highly statistically significant result ($p < 0.001$) on a secondary endpoint using a validated direct physician assessment of motor function in gMG subjects (change from baseline on the Quantitative Myasthenia Gravis (QMG) score). 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 pharmacodynamic/mechanistic data and knowledge of other drugs in the class, appropriate to support approval.

The available safety data show that risks of rozanolixizumab 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 rare chronic autoimmune neuromuscular disease. A systematic review and metaanalysis of published literature estimated the worldwide prevalence of MG to be 12.4 people per 100,000 population (Salari et al. 2021). In the United States, the prevalence is estimated at 14 to 20 per 100,000 population equating to approximately 36,000 to 60,000 patients in the country (MGFA 2015). However, the prevalence in the real world may be higher as MG remains underdiagnosed. At disease onset, some patients experience isolated ptosis and diplopia known as ocular myasthenia gravis. Patients with generalized myasthenia gravis experience weakness in other distributions such as bulbar, axial, limb, and respiratory muscles. - MG is caused by antibodies that bind to functional proteins at the neuromuscular junction. A large majority of patients have detectable antibodies against the acetylcholine receptor (AChR; 80% of patients), whereas less than 10% of patients have antibodies against muscle-specific kinase (MuSK). Antibodies are not detected in 10 to 15% of patients. The anti-AChR antibodies cause damage of the postsynaptic membrane at the neuromuscular junction by activating the complement cascade and antigenic modulation. Anti-MuSK antibodies lead to a reduced density and impaired alignment of AChR in the postsynaptic membrane at the neuromuscular junction. The resulting loss of AChR	MG is a rare, serious, life-threatening disease that can cause disability due to muscle 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
	impairs neuromuscular transmission, which manifest as fatigable muscle weakness. • Women are more often affected than men, with a female to male ratio of 3:1 for anti-AChR-MG and 9:1 for anti-MuSK-MG. Typically, MG affects young adult women (under 40 years of age) and older men (over 60 years of age), but it can occur at any age. Anti-MuSK-MG is predominant in females (>70% of patients) and symptom onset is earlier with a peak of incidence in the 3rd decade. • Typical symptoms of MG may include drooping of eyelids, double vision, inability to reflect emotion due to facial weakness, trouble in swallowing, breathing, and speaking, and muscle weakness in the neck, upper and lower limbs. Life-threatening bulbar and respiratory muscle weakness (MG crisis) occurs in 20% of patients with anti-AChR-MG that requires immediate emergency medical care. In contrast, up to 80% of patients with anti-MuSK-MG have acute onset of bulbar involvement with rapid deterioration, frequently progressing to respiratory failure. Atypical clinical features such as head drop related to neck extensor weakness, muscle atrophy, and absence of typical fluctuation in MG symptoms can make the diagnosis challenging in patients with anti-MuSK-MG. • The diagnosis of MG is based on the clinical presentation, the presence of autoantibodies (anti-AChR, anti-MuSK, and others), and neurophysiological tests such as repetitive nerve stimulation and single-fiber electromyography.	
Current treatment options	• Available treatments include acetylcholine esterase inhibitors such as pyridostigmine bromide, which is FDA-approved for MG. Immunosuppressive treatments such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, and plasmapheresis and intravenous immunoglobulin (IVIg) are used off-label. Thymectomy is also a treatment option for some patients. • Intravenous complement inhibitor monoclonal antibodies, eculizumab (Soliris) and ravulizumab (Ultomiris), have	There remains a significant unmet clinical need for effective treatments for MG because not all patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Corticosteroids, broadly recognized as a mainstay therapy for MG have a rapid action, are inexpensive, and usually result in benefit to patients with MG. However, patients often develop intolerable side effects. Nonsteroidal immunosuppressant treatments may have a delayed response and significant side

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	been FDA-approved for the treatment of patients with anti-AChR-gMG, although their drug labels carry a boxed warning for serious meningococcal infections and have an associated Risk Evaluation and Mitigation Strategy. More recently intravenous efgartigimod (Vyvgart), an Immunoglobulin G subclass 1 fragment crystallizable neonatal fragment crystallizable receptor has been FDA-approved for the treatment of patients with anti-AChR-gMG, with warnings and precautions for infections and hypersensitivity reactions. There are no FDA-approved biologics for anti-MuSK-MG. Furthermore, the symptomatic treatment with acetylcholine esterase inhibitors may be associated with poor tolerance due to side effects in patients with anti-MuSK-MG. Steroids and nonsteroidal immunosuppressant drugs (azathioprine, mycophenolate, tacrolimus, methotrexate, and cyclosporine, rituximab) have been used in patients with anti-MuSK-MG; however, it is often challenging to achieve a long-term effective remission. About 10 to 15% of these patients do not respond to steroids or other immunosuppressant treatment.	effects. Many patients have inadequate response to steroids and nonsteroidal immunosuppressant treatment, with persistent and disabling muscle weakness, and disease relapses which may progress to MG crisis. Plasma exchange and intravenous immunoglobulin (IVIg) are used in patients with acute severe MG as their effect is rapid but short-lived.
Benefit	The efficacy of rozanolixizumab was evaluated in Study MG0003, a 14-week, phase 3, double-blind, placebo-controlled, multicenter (81 sites across 15 countries) study that enrolled 200 adults (≥18 years of age) with the anti-AChR or anti-MuSK seropositive generalized MG (gMG) who experienced moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA II-Iva]) and were being considered for additional treatment such as IVIg or plasma exchange. Subjects were randomized and stratified by the presence of the anti-AChR or anti-MuSK autoantibodies. The subjects were randomized 1:1:1, including two weight-tier based dose arms of rozanolixizumab (approximately 7 mg/kg and 10 mg/kg bodyweight) and one placebo arm (0.9% sodium chloride aqueous solution or physiological saline, preservative free). The study had a 6-week treatment cycle of once	The 14-week randomized double-blind, placebo-controlled study of rozanolixizumab provided reliable and statistically persuasive evidence that rozanolixizumab can help patients with anti-AChR or anti-MuSK antibody positive gMG achieve a clinically meaningful improvement in the symptoms of the disease that affect their activities of daily living, motor function, and disease severity. The study population of 16 subjects with anti-MuSK antibody positive gMG comprised 8% of the total 200 subjects based on the testing at baseline visit, which is consistent with the disease prevalence in the intended patient population (Gilhus et al. 2019). Despite the small number of subjects with anti-MuSK-gMG, there was a clear signal favoring rozanolixizumab for a clinically meaningful improvement in the symptoms of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weekly subcutaneous infusion of either doses of rozanolixizumab or placebo followed by an 8-week blinded observation period. Efficacy was assessed 43 days after the initiation of treatment. - The primary efficacy endpoint was change from baseline to day 43 in MG-specific Activities of Daily Living (MG-ADL) score after the 6-week treatment cycle in the anti-AChR or anti-MuSK seropositive gMG subject population. - A key secondary endpoint was change from baseline to day 43 in the quantitative myasthenia gravis (QMG) score after the 6-week treatment cycle in the anti-AChR or anti-MuSK seropositive gMG subject population. - In Study MG0003, for all subjects with either anti-AChR-gMG or anti-MuSK-gMG, there was a statistically and clinically meaningful change favoring rozanolixizumab in the mean MG-ADL score (rozanolixizumab, -3.4 points for both doses versus placebo, -0.8 points; $p < 0.001$). - For all subjects with either anti-AChR-gMG or anti-MuSK-gMG, there was also statistically and clinically meaningful change favoring rozanolixizumab in the mean quantitative myasthenia gravis score (rozanolixizumab, -5.4 and -6.7 points for ≈ 7 mg/kg and ≈ 10 mg/kg doses, respectively versus placebo, -1.9 points; $p < 0.001$). - Changes from baseline in MG-ADL score to day 43 of rozanolixizumab of ≈ 7 mg/kg dose level and rozanolixizumab of ≈ 10 mg/kg dose level compared to placebo in subjects with gMG were generally consistent across subgroups of anti-AChR and anti-MuSK autoantibody status. - For subjects with anti-MuSK-gMG ($n=16$), eight subjects were randomized to placebo and four subject each to rozanolixizumab ≈ 7 mg/kg dose and rozanolixizumab ≈ 10 mg/kg dose arms. There was a clinically meaningful change favoring rozanolixizumab in the mean MG-ADL score (rozanolixizumab, -6.3 and -4.2 points for ≈ 7 mg/kg and ≈ 10 mg/kg doses, respectively versus placebo, -0.04 points).	disease that affect their activities of daily living, motor function, and disease severity. Because the sample size is small, the effectiveness of rozanolixizumab in patients 65 years of age and older is not adequately established based on the studies included in the BLA. The proposed drug label states that rozanolixizumab should only be prepared and infused by a healthcare provider. Compared to intravenous drug delivery, subcutaneous administration may help reduce patient treatment burden and drug delivery-related healthcare cost and resources use, and in general, it is preferred by both patients and healthcare providers. The potential role of rozanolixizumab for the treatment of patients with seronegative MG and those with purely ocular MG or severe MG who had MG crisis or impending MG crisis is unclear because these patients were not evaluated in the clinical studies included in this BLA submission.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- For subjects with anti-MuSK-gMG, there was also a clinically meaningful change favoring rozanolixizumab in the mean QMG score (rozanolixizumab, -10.3 and -5.1 points for ≈ 7 mg/kg and ≈ 10 mg/kg doses, respectively versus placebo, -2.7 points) and MG-C score (rozanolixizumab, -9.1 and -4.1 points for ≈ 7 mg/kg and ≈ 10 mg/kg doses, respectively; placebo, -2.6 points). - In Study MG0003, none of the subjects required rescue therapy while receiving rozanolixizumab, whereas three subjects (4.5%) in the placebo group needed rescue therapy (IVIg) during the treatment period. A large majority (n=180 out of 191; 94.2%) of the subjects who were on concomitant medications including steroids, nonsteroidal immunosuppressant drugs, and acetylcholine esterase inhibitor drugs at the baseline visit did not require any changes in the dose, frequency, addition, or removal of the MG standard of care during the double-blind treatment period. Three subjects receiving placebo required addition of a concomitant drug in the placebo-controlled treatment period. - A total of 49 (25%) subjects, 65 years and older, were enrolled in the clinical studies of rozanolixizumab. Of these, 46 (94%) subjects had anti-AChR-gMG and the remaining 3 (6%) subjects had anti-MuSK-gMG. In Study MG0003, there were 16 subjects randomized to placebo and rozanolixizumab ≈ 10 mg/kg dose arm each and 17 subjects were randomized to rozanolixizumab ≈ 7 mg/kg dose arm. Out of 33 subjects treated with rozanolixizumab, only one subject had anti-MuSK-gMG. There was an improvement in MG-ADL score with rozanolixizumab compared to placebo from baseline at day 43. - There were consistent changes from baseline at day 43 in MG-ADL score favoring rozanolixizumab across subgroups of sex, bodyweight >50 kg, and geographical regions (United States versus Non-United States). All of	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	these subgroup analyses showed improvement in MG-ADL.	
Risk and risk management	- The safety database (Safety Pool S1; Studies MG0003, MG0004 [first 6 weeks of treatment], and MG0007) included 196 subjects with gMG who were anti-AChR antibody-positive or anti-MuSK antibody-positive exposed to at least one dose of rozanolixizumab. A total of 133 subjects completed more than 12 months in these studies. Of these 133 subjects, 100 (75.2%) subjects had at least 4 treatment cycles of rozanolixizumab, and 88 (66.1%) subjects had at least 5 treatment cycles, which is the maximum number of cycles possible per one year, as per the protocol. The minimum time to initiate subsequent treatment cycle as defined by the protocol in the open-label extension Study MG0007 was 63 days (9 weeks) from the start of the previous treatment cycle. <u>Safety Concerns</u> - Treatment-emergent adverse event (TEAE) with fatal outcome: There were five deaths in the safety database of 196 subjects. All deaths occurred in the open-label extension Study MG0007. Three deaths occurred in the setting of infection. Two deaths attributed to coronavirus disease of 2019 (COVID-19) occurred in subjects receiving rozanolixizumab ≈10 mg/kg. One death was due to multilobar pneumonia in which no pathogen could be identified. Two deaths attributed to cardiac events occurred during the follow-up period or intermittent period between MG0004 and MG0007. - A serious adverse event (SAE) of aseptic meningitis occurred in 1 (0.005%) subject out of total 196 subjects treated with rozanolixizumab. The subject experienced headache, nuchal rigidity, diarrhea, nausea, vomiting, and fever 1.5 days after the first infusion of rozanolixizumab ≈10 mg/kg dose (MG0007). The cerebrospinal fluid was notable for lymphocytic pleocytosis, normal protein, and	The safety database is adequate in terms of size and dosing given that generalized MG is a rare disease. Approval should be accompanied by labeling language to alert the prescriber to the risks of headache, aseptic meningitis, infections, gastrointestinal adverse events, and hypersensitivity reactions. The safety of initiating subsequent treatment cycles sooner than 63 days (9 weeks) from the start of the previous cycle has not been established for rozanolixizumab. Headaches including severe and serious headaches have been reported. A serious case of aseptic meningitis has been reported. Whereas a lumbar puncture was not performed in all subjects who experienced severe headaches, there was an increased frequency of associated symptoms such as fevers, neck pain, nausea, and vomiting. A Warnings and Precautions statement would alert patients and providers to this risk. There was an imbalance between rozanolixizumab (≈10 mg/kg dose level) and placebo in adverse events related to infection, including events related to respiratory tract infection and herpes simplex. Uncertainty exists in whether outcomes of infections would be more serious in an unmonitored outpatient setting or in patients with greater risk for immunosuppression. Warning and Precautions statement for infections will 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. Hypersensitivity reactions, including potentially serious angioedema, and local reactions at the site of administration have been reported. A Warnings and Precautions statement would alert patients and providers to this risk. Gastrointestinal adverse events including serious and severe diarrhea, vomiting, and abdominal pain have been reported. A

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	negative infectious disease work up. The SAE resolved in 5 days after onset and was considered severe. The subject discontinued from the study. - There have been two additional cases of aseptic meningitis in studies evaluating rozanolixizumab for the treatment of myelin oligodendrocyte glycoprotein antibody disease (MOG-AD), (b) (4). Both subjects experienced symptoms of headache and fevers within 2 days after the first infusion (rozanolixizumab 560 mg or placebo) and the event resolved without sequelae. - Common TEAEs: In the phase 3 double-blind, placebo-controlled Study MG0003, the most frequently reported TEAEs (≥5% of subjects in the rozanolixizumab arm and more frequently than placebo) were headache (up to 48%), pyrexia (up to 22%), infections such as upper respiratory tract infection (up to 12%) and herpes simplex (up to 6%), gastrointestinal disorders such as diarrhea (up to 25%), nausea (up to 12%), vomiting (up to 6%), and abdominal pain (up to 9%), injection site reactions (up to 9%), skin rash (up to 7%), and arthralgia and myalgia (up to 7%). - Headaches were the most common TEAE in rozanolixizumab-treated subjects with frequency of 48% at ≈7 mg/kg dose level and 41% at ≈10 mg/kg dose level compared to 19% in the placebo arm in the phase 3 controlled Study MG0003. In most subjects, headaches were of mild or moderate intensity after the first infusion and resolved without sequelae. Seven (5%) subjects experienced severe headache. Of these seven subjects with severe headaches, six were treated with rozanolixizumab ≈10 mg/kg dose and one subject received rozanolixizumab ≈7 mg/kg dose. One subject who received rozanolixizumab ≈10 mg/kg dose had a serious headache requiring hospitalization. One subject discontinued rozanolixizumab ≈7 mg/kg dose due to headache. In Safety Pool S1, out of 196 subjects treated	potentially serious MG exacerbation associated with severe vomiting was reported. Because treatment with rozanolixizumab is associated with reductions in serum IgG levels and increased frequency of infections, a Warnings and Precautions statement in labeling will highlight that the safety of immunization with live-attenuated or live vaccines and the response to immunization with any vaccine is unknown during treatment with rozanolixizumab, and that patients should be vaccinated with age-appropriate vaccinations according to immunization guidelines before starting treatment with rozanolixizumab. Because the risk of adverse outcomes in pregnancy has not been characterized, and because rozanolixizumab 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with rozanolixizumab, 98 (50%) subjects experienced headaches and had associated symptoms of fever (30.6%), nausea (28.6%), vomiting (10.2%) and neck pain (6.1%). There were five events of severe headaches in subjects receiving rozanolixizumab $\approx$7 mg/kg dose level (n=2) and $\approx$10 mg/kg dose level (n=3) in the open-label Studies MG0004 and MG0007. • Infections occurred at higher frequency in the subjects who received rozanolixizumab at $\approx$10 mg/kg dose level (30%) than the lower dose level of 7 mg/kg (16%) and placebo (19%) in the phase 3 controlled Study MG0003. There were no severe or serious infections in the phase 3 controlled Study MG0003. In Safety Pool S1, out of 196 subjects treated with rozanolixizumab, 94 (48%) subjects reported TEAEs of infections and consistent with the controlled study, the rate of infections was relatively higher in the $\approx$10 mg/kg dose arm (55%) compared to $\approx$7 mg/kg dose arm (40%). The most common infections in the safety database were upper respiratory tract infections (17%), COVID-19 (14%), urinary tract infections (9%), and herpes simplex (6%). There were three deaths related to pneumonia including two cases due to COVID-19 and one case due to an unidentified pathogen. Serious infections occurred in 8 (4.1%) subjects including COVID-19 (n=4), aseptic meningitis (n=1), pneumonia (n=1), complicated appendicitis, cholecystitis, peritonitis, and liver abscess (n=1), and E. coli urosepsis (n=1) during an open-label Study MG0007. Rozanolixizumab was discontinued in six (3.1%) subjects due to adverse events of infection. Treatment with rozanolixizumab was associated with reduction in serum IgG levels (<2 g/L; 42.8% versus 0%) as compared to placebo-treated subjects. • Gastrointestinal adverse events of diarrhea, nausea, vomiting, and abdominal pain were frequently observed in the subjects treated with rozanolixizumab. Most of these events were nonserious and of mild or moderate intensity.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Four (3%) subjects out of 133 subjects treated with rozanolixizumab in the phase 3 controlled Study MG0003 had treatment interruption (n=2) and permanent discontinuation (n=2) due to severe or serious vomiting, diarrhea, and abdominal pain. One subject had MG exacerbation because the subject vomited his usual dose of pyridostigmine. In Safety Pool S1, 89 (45%) subjects out of 196 subjects treated with rozanolixizumab experienced gastrointestinal adverse events with the frequency balanced between doses. The event of diarrhea was the most common (32%) followed by nausea (17%), abdominal pain (15%), and vomiting (8%). Most events were of mild or moderate maximum intensity. There were no severe or serious events in the open-label Study MG0007. There were no treatment interruptions or discontinuation due to the gastrointestinal events in Study MG0007. - Hypersensitivity reactions, including skin rash, angioedema, pruritis as well as, local injection site reactions such as rash, erythema, pain, and pruritis were observed in rozanolixizumab-treated subjects. There were no severe or serious reactions. One subject discontinued rozanolixizumab due to pruritis. <u>Other Uncertainties</u> - The risk of serious outcomes such as infections in the postmarketing period, when patients are likely to be observed less frequently than clinical studies is unknown. - The risk of adverse outcomes in pregnancy and potential harm to fetus have not been characterized. The risk of adverse effects on the breastfed infant is unknown. - Because individuals with hepatitis B surface antigen and hepatitis C antibody, and those with tuberculosis or latent tuberculosis infection were not evaluated in the clinical studies, the risk of reactivation of viral hepatitis and tuberculosis with rozanolixizumab is unknown.	

BLA 761286

Rystiggo (rozanolixizumab)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Given the short duration of the clinical studies, the risk of malignancy has not been characterized.	

Abbreviations: AChR, acetylcholine receptor; COVID-19, coronavirus disease of 2019; gMG, generalized myasthenia gravis; IGRA, Interferon gamma release; IVIG, immunoglobulin; MG, Myasthenia Gravis; MG-ADL, myasthenia gravis activities of daily living; MuSK, muscle-specific kinase; SAE, serious adverse event; TEAE, treatment-emergent adverse event

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 because not all MG patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Currently, there are two FDA-approved C5 inhibitors (eculizumab and ravulizumab) and one neonatal fragment crystallizable receptor (FcRn) blocker (efgartigimod) for intravenous administration in the treatment of adult patients with gMG who are anti-AChR antibody positive. Rozanolixizumab is a subcutaneously administered, humanized immunoglobulin G subclass 4 monoclonal antibody that inhibits FcRn, thereby reducing the effective general IgG pool which includes MG-specific autoantibodies.

The Applicant has demonstrated the efficacy of rozanolixizumab for the treatment of gMG in patients who have anti-AChR antibody or anti-MuSK antibody in Study MG0003. This study was a randomized double-blind, placebo-controlled, multicenter study that enrolled 200 subjects with gMG who were on stable dose of AChE inhibitors, corticosteroids, or nonsteroidal immunosuppressive drugs. Subjects received a 6-week treatment cycle of weekly subcutaneous infusions of either rozanolixizumab ≈ 7 mg/kg dose or rozanolixizumab ≈ 10 mg/kg dose or placebo, with efficacy assessed 43 days after the initiation of treatment. Subjects were followed for 8 weeks after the end of the treatment cycle. The primary and the key secondary endpoints were accepted by the Division as clinically meaningful endpoints, and were used in labeling for efgartigimod, ravulizumab, and eculizumab. The Applicant has demonstrated a statistically significant and clinically meaningful effect on the primary endpoint, change from baseline in the myasthenia gravis activities of daily living (MG-ADL) total score (patient-reported outcome [PRO]) and the key secondary endpoint, change from baseline in the quantitative myasthenia gravis (QMG) total score (clinician-reported outcome [ClinRO]) at day 43 after the initiation of the treatment cycle ($p < 0.001$). There was an improvement (decrease) in the MG-ADL least squares mean total score by 3.4 points in the subjects treated with rozanolixizumab at both dose levels compared with a decrease of 0.8 points in the placebo group. Efficacy was supported by improvement (decrease) in the QMG least squares mean total score by -5.4 and -6.7 points in the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg dose, respectively compared with a decrease of 1.9 points in the placebo group.

The Applicant is seeking an indication for the treatment of adults with gMG who are anti-AChR or anti-MuSK antibody positive. The phase 3 study (MG0003) of rozanolixizumab enrolled 179 (89.5%) subjects with anti-AChR-gMG and 21 (10.5%) subjects with anti-MuSK-MG, which is consistent with the disease prevalence ([Gilhus et al. 2019](#)). Although the data are limited by the number of subjects with anti-MuSK-MG, treatment with rozanolixizumab in this population resulted in improvement in the MG-ADL and QMG scores compared to placebo, supporting the clinical efficacy of rozanolixizumab in this rarer form of gMG.

Study MG0003 was an adequate and well-controlled, multicenter study that provides reliable and persuasive evidence that rozanolixizumab benefits adult patients with gMG who are anti-AChR or anti-MuSK antibody positive to achieve a clinically meaningful improvement in the symptoms of MG that affect their activities of daily living. Consistent and distinct treatment effects on the

MG-ADL and the QMG confirm that the observed treatment differences between rozanolixizumab and placebo were highly clinically meaningful and not due to chance. Study MG0003 was large given the size of the patient population. No single site provided an unusually large proportion of subjects, and no site was disproportionately responsible for the observed treatment effect. These findings were statistically robust to sensitivity analyses and generalizable across demographic subgroups of age, sex, body weight, and region of the world. Additionally, pharmacodynamic and mechanistic data relevant to the pathophysiology of MG, reduction in anti-AChR and anti-MuSK antibodies, provide confirmatory evidence to support approval. There is also existing evidence for the effectiveness of the FcRn blocking mechanism in the treatment of gMG with the approval of efgartigimod for the treatment of adults with gMG who are anti-AChR antibody positive (FDA approved in 2021) ([Argenx 2021](#)). Therefore, the study is capable of serving as a single adequate and well-controlled clinical study plus confirmatory evidence to establish substantial evidence of effectiveness of rozanolixizumab treatment in adult patients with gMG who are anti-AChR or anti-MuSK antibody positive.

The safety database for rozanolixizumab was adequate for the intended population and proposed dosing regimen. The safety database for gMG was characterized in a single, double-blind, placebo-controlled study (MG0003) and two open-label extension studies: Studies MG0004 and MG0007 (to capture the safety of repeated cycles of treatment). Common adverse events included headache, infection, diarrhea, nausea, abdominal pain, hypersensitivity reactions, and local administration site reactions. Serious adverse events of infections, aseptic meningitis, headache, vomiting, and gastritis were reported in subjects treated with rozanolixizumab which required hospitalization and treatment discontinuation or interruptions. Safety findings observed during the study can be adequately addressed through labeling and through routine and enhanced pharmacovigilance. Warning and Precautions statements include infections, aseptic meningitis, hypersensitivity reactions, and vaccination-related concerns. Enhanced pharmacovigilance will be requested for serious adverse events related to infections, reactivation of latent tuberculosis and hepatitis B, and malignancies. A pregnancy outcomes study is recommended as a postmarketing requirement.

Based on the review of all available efficacy and safety data, the benefits of rozanolixizumab outweigh the risks for the treatment of adult patients with gMG who are anti-AChR or anti-MuSK antibody positive. The availability of rozanolixizumab will provide a new and effective treatment option via weekly subcutaneous infusion in 6-week symptom-driven treatment cycles for anti-AChR-gMG and anti-MuSK-gMG.

II. Interdisciplinary Assessment

3. Introduction

Myasthenia gravis (MG) is a rare antibody-mediated autoimmune neuromuscular disease. The incidence and prevalence of MG varies across geographical regions. Patient with myasthenia gravis can be classified according to clinical features of the disease. Approximately two-thirds of patients will present with diplopia and ptosis and other symptoms restricted to the ocular muscles. Patients with generalized myasthenia gravis (gMG) experience weakness in other distributions such as bulbar, axial, limb, and respiratory muscles. Myasthenic crisis is a severe life-threatening presentation of gMG, which requires intensive care, ventilation support, and enteral feeding. A systematic review and metanalysis of published literature estimated the worldwide prevalence of MG to be 12.4 people per 100,000 population ([Salari et al. 2021](#)). In the United States, the prevalence is estimated at 14 to 20 per 100,000 population equating to approximately 36,000 to 60,000 patients in the country ([MGFA 2015](#)). However, the prevalence in the real world may be higher as MG remains underdiagnosed.

A majority (80%) of patients with gMG have detectable antibodies against acetylcholine receptor (AChR), the major cation channel at the postsynaptic membrane of the NMJ. About 1 to 10 percent of total gMG patients (30 to 50 percent of patients with anti-AChR antibody seronegative gMG) have antibodies against muscle-specific kinase (MuSK), which is responsible for clustering of the AChR at the postsynaptic membrane of the neuromuscular junction (NMJ) ([Gilhus et al. 2019](#)). The anti-AChR antibody response is polyclonal and activates the complement cascade upon antigen binding, leading to the formation of the membrane attack complex and damage of the postsynaptic membrane at the NMJ. The anti-AChR antibodies induce antigenic modulation, with increased internalization and destruction of the AChR through receptor crosslinking by bivalent antibodies. Most anti-MuSK antibodies are of the functionally monovalent IgG4 subclass. The anti-MuSK antibodies are unable to activate complement and induce antigenic modulation. These antibodies inhibit MuSK function and lead to reduced AChR density and alignment at the postsynaptic membrane. Anti-MuSK-MG is predominant in females (>70% of patients) and symptom onset is earlier with a peak of incidence in the third decade. The disease has typically acute onset of bulbar involvement (up to 80% of patients) with rapid deterioration, frequently progressing to respiratory failure. These patients have a higher risk of MG crisis. Head drop related to neck extensor weakness, muscle atrophy, and absence of typical fluctuation in MG symptoms can make the diagnosis challenging.

There remains a significant unmet clinical need for effective treatments for gMG because not all patients are able to receive, tolerate, or adequately benefit from the available clinical treatments. Currently, patients with gMG have an option of symptomatic treatment with acetylcholine esterase (AChE) inhibitors such as FDA-approved pyridostigmine bromide, immunosuppressive treatment (off-label) such as steroids and nonsteroidal immunosuppressants, and plasma exchange or intravenous immunoglobulin therapy (also off-label). However, patients often experience intolerable side effects. Up to 30% of patients have inadequate response to steroids and nonsteroidal immunosuppressant treatment, with persistent and disabling muscle weakness,

and disease relapses which may progress to MG crisis. There are no FDA-approved biologics for patients with anti-MuSK-gMG. Three biologics, including eculizumab and ravulizumab, monoclonal antibodies inhibiting complement activation at the C5 protein, and efgartigimod, an immunoglobulin G subclass 1 (IgG1) fragment crystallizable (Fc) fragment targeting FcRn, have been approved for the treatment of patients with anti-AChR-gMG. Steroids and nonsteroidal immunosuppressant drugs (azathioprine, mycophenolate, tacrolimus, methotrexate, and cyclosporine, rituximab) have been used in patients with anti-MuSK-gMG; however, it is often challenging to achieve a long-term effective remission. About 10 to 15% of patients anti-MuSK-gMG do not respond to steroids or other immunosuppressant drugs.

The pivotal Study MG0003 and the open-label Studies MG0004 and MG0007 enrolled adults with gMG who were either anti-AChR or anti-MuSK antibody positive. The studies excluded the seronegative individuals with gMG, those with purely ocular MG, and those with severe weakness affecting oropharyngeal or respiratory muscles, or who had MG crisis or impending crisis.

For this biologics license application (BLA), the investigational drug rozanolixizumab (Rystiggo, UCB7665) is a recombinant, humanized anti-FcRn immunoglobulin G subclass 4 monoclonal antibody (IgG4p) monoclonal antibody. The proposed mechanism of drug action is FcRn inhibition by rozanolixizumab leads to enhanced degradation of immunoglobulin G (IgG), with the aim to reduce pathogenic anti-AChR and anti-MuSK MG-specific autoantibodies. The Applicant's proposed indication for rozanolixizumab is the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive.

Study MG0003 was a phase 3, multinational, randomized, double-blind, placebo-controlled study of rozanolixizumab for the treatment of generalized myasthenia gravis. In the study, subjects were treated for 6-weeks, with once weekly infusions of the investigational product. The total study duration was 14 weeks which included an 8-week observational period. In the open-label Study MG0007, subjects received additional treatment cycles separated by a variable intertreatment length of time depending on a subject's clinical response to rozanolixizumab.

The review team identified three key review issues that impact the overall review of rozanolixizumab and the product labeling.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Efficacy in Anti-AChR and Anti-MuSK Antibody Seropositive Myasthenia Gravis

Evaluate whether the evidence provided by the Applicant supports the proposed indication: adult (b) (4) with gMG who are anti-acetylcholine receptor (anti-AChR) or anti-muscle-specific tyrosine kinase (anti-MuSK) antibody positive.

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

Determine the minimum length of time between treatment cycles of rozanolixizumab that is supported by the available efficacy and safety data.

3.1.1.3. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Determine if the Applicant's proposed 2-fixed dosing regimen of rozanolixizumab for treatment of gMG patients is adequate.

3.1.2. Key Safety Review Issues

3.1.2.1. Infections

3.1.2.2. Headaches

3.1.2.3. Hypersensitivity Reactions

3.1.2.4. Gastrointestinal Disorders

3.1.2.5. Hypoalbuminemia

3.1.2.6. Immunization

3.2. Approach to the Clinical Review

The clinical studies submitted to support the safety and efficacy of rozanolixizumab are summarized below ([Table 3](#)). This BLA submission includes the pivotal phase 3 randomized, double-blind, placebo-controlled study (MG0003) of rozanolixizumab (Rystiggo, UCB7665) in adult subjects with generalized MG who are anti-AChR or anti-MuSK antibody positive and experience moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA II-Iva]). Additional supportive safety data are provided from the first 6-week treatment period in the open-label Study MG0004 and the ongoing open-label extension Study MG0007, including data from the 120-day safety update.

An efficacy determination was made by evaluating the results from Study MG0003. 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 safety data generated by the clinical data scientist and Applicant's submitted data.

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The primary safety data were from Study MG0003 with supportive data from Study MG0004 (first 6 weeks only) and Study MG0007.

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations¹ for Rozanolixizumab

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
MG0003 NCT03971422	Adults with gMG who are anti-AChR or anti-MuSK antibody positive and with Myasthenia Gravis Foundation of America (MGFA) Class II to Iva	Control type: Placebo (0.9% normal saline) Randomization: 1:1:1 stratified by the presence of the anti-AChR or anti-MuSK autoantibodies Blinding: Double-blind	Drug: Rozanolixizumab Dosage: ≈7 mg/kg and ≈10 mg/kg by a weight tier or a matched placebo Number treated: Total n=200; rozanolixizumab ≈7 mg/kg, n=66; ≈10 mg/kg, n=67; placebo, n=67 Duration (quantity and units): once a week subcutaneous infusion for 6 weeks followed by 8-weeks observation period.	Primary: the change from baseline to day 43 in the MG-ADL score after the 6-week treatment cycle Key Secondary: 1. The change from baseline to day 43 in the QMG score after the 6-week treatment cycle 2. The change from baseline to day 43 in the MG-C score after the 6-week treatment cycle	n=200 randomized anti-AChR-Ab positive: 179 anti-MuSK-Ab positive: 21 M =79/F =121	n=81 sites in 15 countries, Canada, Czech Republic, Denmark, France, Georgia, Germany, Hungary, Italy, Japan, Poland, Russian Federation, Serbia, Spain, Taiwan

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Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
MG0004 (first 6-weeks only) NCT04124965	MG0003 completers or subjects requiring rescue therapy during observation period	Control type: none. Open-label extension (OLE) to MG0003 study Randomization: 1:1 Blinding: open-label	Drug: Rozanolixizumab Dosage: ≈7 mg/kg or ≈10 mg/kg by a weight tier Number treated: total n=71; rozanolixizumab ≈7 mg/kg, n=35; ≈10 mg/kg, n=36 Duration (quantity and units): once a week for the first 6 weeks (planned treatment duration up to 52 weeks; study discontinued)	Primary: the occurrence of TEAEs and the occurrence of TEAEs leading to permanent withdrawal of study medication Key Secondary: Change from baseline in the MG-ADL, MG-C, and QMG total scores, use of rescue medication (IVIg or PEX)		N=81 sites in 15 countries (same as MG0003)

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Rystiggo (rozanolixizumab)

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
MG0007 (ongoing, interim data cutoff July 8, 2022) NCT04650854	MG0003 completers or subjects requiring rescue therapy during observation period or subjects who have completed ≥6 treatment visits in MG0004	Control type: OLE to MG0003 study Randomization: 1:1 Blinding: open-label	Drug: Rozanolixizumab Dosage: ≈7 mg/kg or ≈10 mg/kg by a weight tier Number treated: n=165: rozanolixizumab ≈7 mg/kg (n=88) and ≈10 mg/kg (n=77) Duration (quantity and units): once per week subcutaneous infusion for 6 weeks followed by 16-weeks observation period then on demand based on symptom worsening with at least 4-week intervals between cycles. Less than 10% had the interval <4 weeks based on IgG level ≥2 g/L	Primary: the occurrence of TEAEs and the occurrence of TEAEs leading to permanent withdrawal of study medication Key Secondary: Change from baseline in the MG-ADL, MG-C, QMG, and MG-PRO total scores	n=165 from Study MG0003 (n=105) and MG0004 (n=60); M =69/F =96	n=81 sites in 15 countries (same as MG0003)

Source: Reviewer. MG0003 CSR, MG0004 CSR, MG0007 CSR, Module 2.7.4 Summary of Clinical Safety

¹ Includes all submitted clinical studies, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² If no randomization, then replace with "Actual Enrolled."

Abbreviations: AChR, acetyl choline receptor; F, female; gMG, generalized myasthenia gravis; IVIg, intravenous immunoglobulin; M, male; MG-ADL, myasthenia gravis activities of daily living; MG-C, myasthenia gravis composite; MuSK, muscle-specific kinase; N, number of subjects; OLE, open-label extension; PEX, plasma exchange.; PRO, patient-reported outcome; QMG, quantitative myasthenia gravis; TEAE, treatment-emergent adverse event

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2.2.1
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6.2.2.1
☐	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

5.1. Nonclinical Assessment of Potential Effectiveness

The neonatal Fc receptor (FcRn) is a cell surface receptor located on a wide variety of cell types including endothelial cells and hematopoietic cells. This receptor binds endogenous IgG and albumin and prevents their endosomal degradation by releasing them back into circulation. This process of IgG “recycling” results in the observed long half-life of IgG in vivo (IgG $t_{1/2}$ estimated to be 25 days or greater).

UCB7665 (rozanolixizumab), a humanized IgG4 monoclonal antibody directed against the human FcRn, is intended to prevent recycling of IgG, but not albumin. By preventing IgG

recycling, UCB7665 is expected to reduce the level of circulating autoantibodies thought to be involved in the pathogenesis of MG. In vitro and in vivo proof of concept studies were conducted to characterize the pharmacological activity of UCB7665 in cynomolgus monkeys and transgenic mice.

In Vitro

In BIAcore (i.e., plasmon surface resonance) assays, the affinity (K_D) of UCB7665 for human and monkey FcRn were 55 and 57 pM, respectively, at a pH of 7.4 and 44 and 42 pM, respectively, at a pH of 6.0. In Madin-Darby canine kidney (MDCK) cells that expressed human or monkey FcRn, the K_D was 0.43 and 1.03 nM, respectively. Additional studies in the same cell lines indicated inhibition of IgG recycling by human and monkey FcRn and inhibited transcytosis by human FcRn.

In Vivo

UCB7665 was tested in a transgenic mouse model (hFcRnTg) in which the human FcRn is expressed. Single doses of 0, 10, 30, or 100 mg/kg were administered by intravenous (IV) injection 1 day after pre-administration of human IgG. Results indicated a dose-dependent increase in human IgG clearance 24 hours postdose that was sustained until the end of the study (i.e., 192 hours postdose). No significant changes in albumin levels were detected relative to control.

In the general toxicity studies in monkeys in which subcutaneous doses of up to ≈ 150 mg/kg UCB7665 were administered every 3 days for up to 26 weeks, pharmacodynamic effects consisted of reductions in IgG levels with no effects on immunoglobulin A or immunoglobulin M. Albumin was also reduced at the highest doses due to steric blocking of the albumin binding portion of FcRn.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Rozanolixizumab is a recombinant, humanized antineonatal Fc receptor (FcRn) IgG4P monoclonal antibody.
Mechanism of action	Rozanolixizumab decreases serum IgG concentration, including anti-AChR- and anti-MuSK-specific pathogenic IgG by inhibiting the binding of IgG to FcRn (FcRn normally protects IgG from intracellular degradation and recycles IgG back to the cell surface)
Active moieties	Rozanolixizumab
QT prolongation	Dedicated QTc prolongation study was not conducted. Rozanolixizumab is a human IgG4P antibody fragment with a molecular weight of 147 kDa, and no direct ion channel effects are expected.
	General Information
Bioanalysis	The plasma concentrations (in studies UP0018, TP0001 and MG0002) of rozanolixizumab were determined by validated enzyme-linked immunosorbent assay (ELISA) methods and redeveloped for studies CIDP01 and UP0060. 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	At the end of treatment cycle (on day 43) following the sixth weekly dose of ≈ 7 mg/kg or ≈ 10 mg/kg, majority of plasma concentrations were BLQ from Study MG0003.
Range of effective dose(s) or exposure	Two dose-levels, ≈ 7 mg/kg and 10 mg/kg administered Q1W*6 were studied in phase 3 (MG0003) study.
Maximally tolerated dose or exposure	The highest evaluated dose in humans was a single dose of ≈ 20 mg/kg in adults with primary immune thrombocytopenia (ITP) (n=12) in study TP0001.
Dose proportionality	Rozanolixizumab exposure increased in a greater than dose proportional manner following a single subcutaneous dose in the range from ≈ 1 mg/kg to ≈ 20 mg/kg.
Accumulation	Plasma levels at C_{trough} (1 week after dosing) are close to or below the limit of quantification (BLQ) in majority of patients, limiting the ability to calculate terminal half-life, and accumulation.
Time to achieve steady-state	Steady-state exposures of rozanolixizumab are expected to be achieved by the sixth weekly dose, i.e., within end of the treatment of the cycle (Q1W*6).
Bridge between to-be-marketed and clinical study formulations	The final-to-be-marketed (liquid formulation) was used in phase 3 clinical Study MG0003 (pivotal); therefore, no clinical PK-based bridging study is required.

Characteristic	Drug Information
Absorption	
Bioavailability	The absolute bioavailability for the ≈ 7 mg/kg dose was 14%; however, this value should be interpreted with caution given the target mediated drug disposition (TMDD) of rozanolixizumab.
T _{max}	Approximately 2 days postinfusion.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Rozanolixizumab is administered subcutaneously as an infusion (b) (4), and therefore food-effect is not relevant.
Distribution	
Volume of distribution	Based on population PK analyses, the mean estimate of apparent volume of distribution was 6.6L.
Plasma protein binding	Plasma protein binding was not determined.
Drug as substrate of transporters	Rozanolixizumab is a human IgG4 monoclonal antibody 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.
Clearance	Based on population PK analysis, the mean estimate for apparent CL/F was 0.89L/day.
Half-life	Precise half-life was not determined.
Metabolic pathway(s)	Rozanolixizumab is a human IgG4 monoclonal antibody and is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids, which are expected to be excreted or recycled in the same manner as endogenous IgG.
Intrinsic Factors and Specific Populations	
Body weight	In Study MG0003, the Applicant evaluated a weight-tiered regimen in which subjects received once weekly (Q1W) fixed doses (based on specific bodyweight cut-offs), which equate ≈ 7 mg/kg or ≈ 10 mg/kg for 6 weeks (one treatment cycle). Refer to the pharmacometrics review for additional discussion on effect of body weight on PK and PD of rozanolixizumab
Age	No dose adjustment is needed based on age.
Renal impairment	No dose adjustment is needed in patients with renal impairment.
Hepatic impairment	No dose adjustment is needed in patients with hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Rozanolixizumab 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	Rozanolixizumab is a human IgG4 monoclonal 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 medications that bind to the human FcRn (i.e., immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass), when concomitant use is necessary. When concomitant long-term use of such medications is essential for patient care, consider discontinuing rozanolixizumab using alternative gMG medications. Other therapeutic proteins are unlikely to alter the binding of rozanolixizumab to FcRn receptor.

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Rystiggo (rozanolixizumab)

Characteristic	Drug Information
Impact on immunizations	Vaccination with live-attenuated or live vaccines is not recommended during treatment with rozanolixizumab. Administer all age-appropriate vaccines according to immunization guidelines before initiation of treatment of rozanolixizumab.
	<i>Immunogenicity</i>
Bioanalysis	Immunogenicity assessments were conducted using semihomogenous bridging electro-chemiluminescence immunoassay (ECLIA) assay was used to determine levels of antidrug antibodies (ADA), and neutralizing capacity of the ADA.
Incidence	In Study MG0003 following 99 days after last (6 th weekly) dose of rozanolixizumab treatment, the incidence of antidrug antibodies (ADA) was 49/133 (37%) and the incidence of neutralizing antibody was 28/49 (57%)]]. Upon repeating the 6-week dosing cycle for up to five additional cycles in Study MG0007, the antidrug antibody incidence was 44.4% (71/160) and the incidence of neutralizing antibodies was 69% (49/71).
Clinical impact	There's no clinically relevant impact of ADA on efficacy or safety of rozanolixizumab.

Abbreviations: AChR, acetylcholine receptor; ADA, antidrug antibody; BLQ, below limit of quantification; CYP, ; ECLIA, electro-chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; EPC; Fc, fragment crystallizable; FcRn, neonatal fragment crystallizable receptor ; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IgG4, Immunoglobulin G subclass 4; MuSK, muscle-specific kinase; MW, molecular weight; PK, pharmacokinetic; Q1W, once a week; TMDD, target-mediated drug disposition

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted a phase 1 study (UP0018) which was a first in human, randomized, double-blind, placebo-controlled, single ascending dose study in adult healthy volunteers. The subjects (randomized 3:1) received ≈ 1 mg/kg, ≈ 4 mg/kg, or ≈ 7 mg/kg either IV or SC as a one-hour infusion. Pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity (total IgG reduction) data were collected. There was a dose-dependent decrease in total IgG levels. Further, the Applicant noted that the mean maximum percentage reduction in total IgG concentrations after single doses of IV and SC treatment of ≈ 7 mg/kg was 49% and 44%, respectively. In another phase 1 study (UP0060) which was a randomized, double-blind, placebo-controlled study in adult healthy volunteers, three dose levels were studied: cohort 1 (≈ 4 mg/kg), cohort 2 (≈ 7 mg/kg), and cohort 3 (≈ 10 mg/kg). Caucasian, Japanese, and Chinese subjects randomized to rozanolixizumab and placebo. Dose-dependent reductions in total IgG were observed in all ethnicities and there were no major differences across the ethnic populations for the ≈ 7 mg/kg and ≈ 10 mg/kg dose groups.

The Applicant conducted a phase 2 study (MG0002), a multicenter, randomized, double-blind, placebo-controlled, 2-arm, repeat-dose study in moderate to severe gMG patients. In dosing period 1, subjects received either placebo or ≈ 7 mg/kg Q1W for 3 weeks. In dosing period 2, subjects were rerandomized to receive 3 doses of rozanolixizumab at weekly intervals at a dose of ≈ 4 mg/kg or ≈ 7 mg/kg, resulting in 4 treatment groups: placebo-rozanolixizumab ≈ 7 mg/kg, placebo-rozanolixizumab ≈ 4 mg/kg, rozanolixizumab ≈ 7 mg/kg - ≈ 7 mg/kg, and rozanolixizumab ≈ 7 mg/kg - ≈ 4 mg/kg. In dosing period 1, $\approx 64\%$ reduction was observed in total IgG with the ≈ 7 mg/kg dose compared to placebo. For subjects randomized to rozanolixizumab in both dosing periods, reduction in total IgG levels were higher compared to subjects randomized to placebo in dosing period 1. The ≈ 7 mg/kg - ≈ 7 mg/kg had slightly higher reduction in baseline IgG levels compared to ≈ 7 mg/kg - ≈ 4 mg/kg group (69% versus 64%). The Applicant also reported median maximum percent change of 65% to 75% reduction in pathogenic IgG (anti-AChR autoantibodies) in all dose groups.

Based on the results from phase 1 and 2 studies and PK modeling and simulations, the Applicant selected ≈ 7 mg/kg and ≈ 10 mg/kg to be administered Q1W for 6 doses for the phase 3 study (MG0003) in moderate to severe gMG patients. Like Study MG0002, a mean maximum reduction of $\approx 75\%$ in total IgG levels was observed. A median maximum reduction of 73% at ≈ 7 mg/kg and 81% at ≈ 10 mg/kg in anti-AChR autoantibodies was observed. The median maximum reduction of 37% at ≈ 7 mg/kg and 56% at ≈ 10 mg/kg in anti-MuSK autoantibodies was observed. These changes in PD response correlated with clinical efficacy response (reduction in MG-ADL scores) after six once-weekly doses.

The Applicant proposed 2-fixed dose regimen: (b) (4) and 420 mg for patients weighing (b) (4) < 50 kg supported by popPK-PD-efficacy modeling. Although the model adequately characterizes the PK/PD profile at ≈ 7 - and ≈ 10 mg/kg dose levels, a

substantial proportion of rozanolixizumab plasma concentrations fall below the lower limit of quantification (LLOQ). In addition, the observed data for the 1 mg/kg dose suggests caution in relying on model predictions for low doses. Therefore, the clinical pharmacology review team expresses caution in the model's ability to accurately predict changes in total IgG and MG-ADL.

Based on these considerations, the review team recommends 420 mg Q1W in patients <50 kg and 560 mg Q1W in patients 50 kg to <100 kg for 6 weeks (i.e., 1 treatment cycle), and 840 mg Q1W in patients 100 or more (discussed in detail in Section 6.3.3). This recommendation is consistent with the weight-tiered dosing regimen evaluated in Study MG0003 in gMG patients. The Applicant concurred with the review team's recommendation, including 840 mg rozanolixizumab dose in patients weighing 100 kg or more.

Furthermore, the clinical pharmacology team has evaluated the proposed instructions by the applicant for delayed or missed dosing and finds them acceptable.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Results of Pooled Analyses

Not applicable.

6.2.2. Study MG0003

6.2.2.1. Design, Study MG0003

Overview and Objective

Study MG0003 was a phase 3, randomized, double-blind, placebo-controlled study of rozanolixizumab (UCB7665) in adult subjects with gMG who are anti-AChR or anti-MuSK antibody positive and experience moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA] Class II-Iva).

The primary objective was to evaluate the clinical efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in MG-ADL score after the 6-week treatment cycle in the anti-AChR or anti-MuSK seropositive gMG subject population.

The secondary objectives are listed below:

- To evaluate the efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in the myasthenia gravis composite (MG-C) score in the anti-AChR or anti-MuSK seropositive gMG subject population
- To evaluate the efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in the QMG score in the anti-AChR or anti-MuSK seropositive gMG subject population

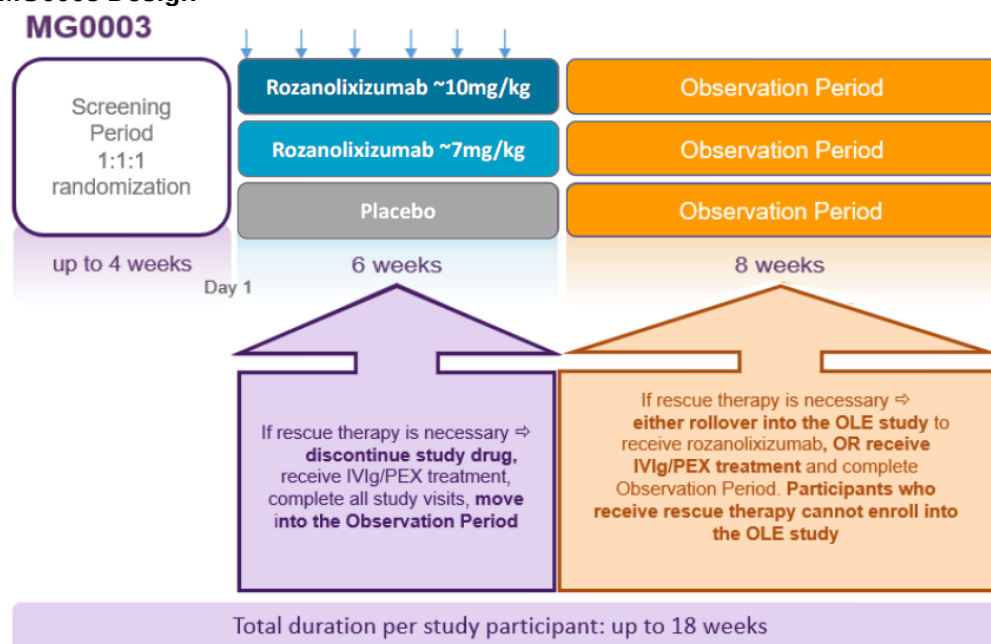
- To evaluate the efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in the MG Symptoms PRO Domain “muscle weakness fatigability” score in the anti-AChR or anti-MuSK seropositive gMG subject population
- To evaluate the efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in the MG Symptoms PRO Domain “physical fatigue” score in the anti-AChR or anti-MuSK seropositive gMG subject population
- To evaluate the efficacy of rozanolixizumab as assessed by the change from baseline to day 43 in the MG Symptoms PRO Domain “bulbar symptoms” score in the anti-AChR or anti-MuSK seropositive gMG subject population

Basic Study Design

Study MG0003 was a multicenter (n=81 sites), multinational (15 countries: Canada, Czech Republic, Denmark, France, Georgia, Germany, Hungary, Italy, Japan, Poland, Russian Federation, Serbia, Spain, Taiwan), randomized, double-blind, placebo-controlled, 3-arm study which included two active-dose arms (approximately 7 mg/kg and 10 mg/kg bodyweight), and one placebo arm (0.9% sodium chloride aqueous solution or physiological saline, preservative free), phase 3 study in adults (≥ 18 years of age) with the anti-AChR or anti-MuSK seropositive gMG who experience moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA] Class II-Iva) and are being considered for additional treatment such as intravenous immunoglobulin (IVIg) or plasma exchange (PEX). Subjects were randomized and stratified by the presence of the anti-AChR or anti-MuSK autoantibodies. An independent data monitoring committee (IDMC) monitored the ongoing safety and efficacy of the study.

The total study duration was up to 18 weeks and included a 4-week screening period and a 6-week treatment period followed by an 8-week blinded observation period. During the treatment period, rozanolixizumab or placebo were administered subcutaneously once a week for 6 weeks. All eligible study subjects who completed the observation period could be rerandomized into an open-label extension (OLE) study to either active dose arm 1 or 2. The study design is shown in [Figure 1](#).

Figure 1. Study MG0003 Design



IVIg=intravenous immunoglobulin G; OLE=open-label extension; PEX=plasma exchange

Source: BLA Submission Module 2.7.3 Figure 1-1, Page 15, dated October 18, 2022

Abbreviations: BLA, biologics license application; IVIG, immunoglobulin; MG, myasthenia gravis; OLE, open-label extension; PEX, plasma exchange

Rozanolixizumab was administered subcutaneously at doses ≈ 7 mg/kg and ≈ 10 mg/kg based on a body weight-tiered approach with five different fixed doses across four body weight tiers (Table 6). The Applicant has proposed a 2-fixed dosing strategy for rozanolixizumab in the draft label and has submitted subgroup analysis by weight tier and administered dose for the primary and secondary endpoints in the pivotal Study MG0003.

Table 6. Rozanolixizumab Dosages for the Randomized Treatment Period in Study MG0003

Body weight	RLZ subcutaneous dose	
	≈ 7 mg/kg	≈ 10 mg/kg
≥ 35 to < 50 kg	280mg	420mg
≥ 50 to < 70 kg	420mg	560mg
≥ 70 to < 100 kg	560mg	840mg
≥ 100 kg	840mg	1120mg

$\approx$ approximate dose; RLZ=rozanolixizumab

Source: BLA Submission Module 2.7.3 Section 1.2.1, Table 1-1 on Page 13

Abbreviations: RLZ, rozanolixizumab

Study subjects who experienced disease worsening during the 6-week treatment period (e.g., an increase of two points on the MG-ADL or three points on the QMG scale between two consecutive visits) were considered for rescue therapy (IVIg or PEX) at the discretion of the

investigator. No further infusions of rozanolixizumab were administered after initiation of rescue therapy. These subjects completed all study visits including the 8-week observation period.

Study subjects who completed the treatment period and required initiation of rescue therapy after they started the 8-week observation period were either eligible to receive IVIg or PEX or complete the end of study visit and immediately roll over into an OLE study where the subject received rozanolixizumab. Study subjects who opted to receive IVIg or PEX completed any remaining visits in the observation period and did not enter the OLE study.

A schedule of events is provided in [Table 7](#).

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Table 7. Study MG0003 Schedule of Events

Procedure	Screening	Treatment Period									Observation Period			
Visit	V1	V2 (BL)	V3 ^a	V4	V5	V6	V7 ^a	V8	V9	V10 (EOT or PEOT)	V11 ^b	V12	V13 ^b	V14 (EOS)
Day (days) ^c	-28 to -1	1	3(±1)	8(±2)	15(±2)	22(±2)	24(±1)	29(±2)	36(±2)	43(±2)	57(±3)	71(±4)	85(±3)	99(±4)
Written informed consent	X													
Optional PK sub-study consent ^d	X													
Demographic and Baseline ^e	X	X												
Verification of inclusion/exclusion criteria	X	X												
Prior and concomitant medications and medical procedures	X	X		X	X	X		X	X	X	X	X	X	X
General medical history	X													
Psychiatric history/C-SSRS	X													
Query for suicidality ^f		X		X	X	X		X	X	X		X		X
Chest X-ray ^g	X													
IGRA TB test ^h	X													
TB Signs and Symptoms questionnaire	X	X								X				X
12-lead ECG	X	X		X						X				X
Full physical examination	X	X								X		X		X
Brief physical examination				X	X	X		X	X					
Pregnancy test (serum)	X													
Pregnancy test (urine) ⁱ		X						X						X
Hematology, serum chemistry, urinalysis	X	X		X		X			X	X		X		X

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Procedure	Screening	Treatment Period									Observation Period			
Visit	V1	V2 (BL)	V3 ^a	V4	V5	V6	V7 ^a	V8	V9	V10 (EOT or PEOT)	V11 ^b	V12	V13 ^b	V14 (EOS)
Day (days) ^c	-28 to -1	1	3(±1)	8(±2)	15(±2)	22(±2)	24(±1)	29(±2)	36(±2)	43(±2)	57(±3)	71(±4)	85(±3)	99(±4)
PTT and INR measurements	X	X												X
Serology testing for HIV, Hepatitis B, and Hepatitis C	X													
Anti-tetanus toxoid titer		X								X				X
Vital signs	X	X	X	X	X	X	X	X	X	X		X		X
Call or enter IRT to register the visit	X			X	X	X		X	X	X				X
Call or enter IRT/ Randomization		X												
Study participants identification card assigned		X												
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration ^l		X		X	X	X		X	X					
Blood sampling for PK ^k		X	X		X		X			X				
Blood sampling for ADA	X	X			X		X			X		X		X
Blood sampling for exploratory safety biomarker analysis ^l		X												
Blood sampling for future exploratory biomarker analysis		X		X										X
Blood sampling for total IgG and IgG subclasses	X	X		X	X	X		X	X	X		X		X
Blood sampling for IgA, IgM, IgE		X								X				X
MG-specific autoantibodies ^m		X			X			X		X		X		X
Serum complement levels (C3, C4) and cytokines ⁿ		X							X					
Plasma complement levels (C3a and C5a) ⁿ		X							X					
MGFA classification	X	X								X				X
QMG scale	X	X		X	X	X		X	X	X		X		X
MG-C scale	X	X		X	X	X		X	X	X		X		X
MG-ADL	X	X		X	X	X		X	X	X	X	X	X	X
MG Symptoms PRO	X	X		X	X			X		X		X		X
PGI-S	X	X			X			X				X		X
PGI-C					X			X				X		X
EQ-5D-5L		X								X				
MGII ^o		X								X				
MG-QOL15r		X								X				
Study drug discontinuation criteria				X	X	X		X	X					
Study withdrawal criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AChR=acetylcholine receptor; ADA=anti-drug antibody; AE=adverse event; AESM=adverse events of special monitoring; BL=Baseline; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D-5L; EOS=End of Study; EOT=End of Treatment; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM= immunoglobulin M; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; INR=international normalized ratio; IRT=interactive response technology; MG=myasthenia gravis; MG-ADL=myasthenia gravis-Activities of Daily Living; MG-C=Myasthenia Gravis Composite; MGFA=Myasthenia Gravis Foundation of America; MGII=Myasthenia Gravis Impairment Index; MG-QOL15r=Myasthenia Gravis Quality of Life; MuSK=muscle-specific kinase; PEOT=premature end of treatment; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetics; PTT=partial thromboplastin time; PRO=patient-reported outcome; QMG=Quantitative Myasthenia Gravis; TB=tuberculosis; V=Visit

^a This visit can be scheduled as a home visit, unless the study participant prefers to attend the site.

^b This visit will be a virtual visit, unless the study participant prefers to attend the site.

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- ^c A visit window of ± 1 day is allowed for V3 and V7. A visit window of ± 2 day is allowed for all dosing visits. The visit window of ± 2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose. A visit window of ± 3 days is allowed for V11 and V13. A visit window of ± 4 days is allowed for V12 and V14.
- ^d Refer to Section 1.4.
- ^e Only weight will be repeated at Baseline (V2).
- ^f A full C-SSRS assessment will be performed only when study participant has a positive response to Question 1 of the suicidal ideation query. If a study participant has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the study participant will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional.
- ^g Chest X-ray should only be performed at sites in countries at high risk for TB (see Section 8.2.6). If chest X-ray is performed, the study participant cannot be dosed until the result is available, and negative.
- ^h The IGRA test will be performed in a central laboratory. Study participant should not be dosed in case of any positive IGRA or two indeterminate IGRAs until the study participants has been evaluated by a TB specialist.
- ⁱ Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.
- ^j Study participants must be observed at site postdose for at least 4 hours following the first 2 infusions, and then 2 hours thereafter for subsequent infusions.
- ^k At dosing visits, PK samples should be taken predose for all study participants.
- ^l Additional exploratory safety samples must be collected 4 hours postdose or as soon as possible before the next IMP in case of AESM of severe headache and/or AESM of severe GI disorders as described in Section 8.3.7.
- ^m MuSK and AChR antibodies will be tested at Baseline. All subsequent testing will be limited to the positive antibody.
- ⁿ To be collected predose at V2, and 4 hours postdose at V9. Additional samples should be collected 2 hours and 4 hours postevent or as soon as possible before the next IMP for study participants with severe headache and/or infusion reaction or hypersensitivity reaction.
- ^o MGII is optional for all study participants.

Source: Module 5.3.5.1. MG0003-protocol-amend-4, Section 1.3 dated February 23, 2021.

Primary Efficacy Endpoint for Study MG0003

The primary efficacy endpoint for Study MG0003 was the change from baseline to day 43 in Myasthenia Gravis Activities of Daily Living (MG-ADL) score after the 6-week treatment cycle in the anti-AChR or anti-MuSK seropositive gMG subject population.

The MG-ADL is a categorical subject-reported outcome scale ([Table 8](#)) that assesses the impact on daily function of eight signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0 to 24). Thus, higher scores indicate greater severity of symptoms. The MG-ADL is composed of items related to subjects' assessment of functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items).

Table 8. Myasthenia Gravis Activities of Daily Living (MG-ADL) Scale

Symptom	0	1	2	3	Score (0, 1, 2, 3)
1. Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. 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	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, request assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
MG-ADL total score (items 1–8)					

Source: ([Muppidi et al. 2022](#)).

Reviewer's Comments: *The Division previously agreed with the acceptability of the change from baseline on MG-ADL score as a primary endpoint. The MG-ADL is considered to assess clinically meaningful changes in patient function impacted by gMG. 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, ravulizumab, and efgartigimod for gMG.*

Key Secondary Efficacy Endpoints for Study MG0003

The key secondary endpoints are outlined in [6.2.2.1](#). These included the change from baseline to day 43 in QMG and MG-C scores after the 6-week treatment cycle in the anti-AChR or anti-MuSK seropositive gMG subject population.

The Quantitative Myasthenia Gravis (QMG) is a physician assessment scoring system ([Table 9](#)) 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.

Table 9. Quantitative Myasthenia Gravis (QMG) Score

Test Items Weakness	None	Mild	Moderate	Severe
Double vision on lateral gaze right or left (circle one)	61	11–60	1–10	spontaneous
Ptosis (upward gaze)	61	11–60	1–10	spontaneous
Facial muscles	normal lid	complete, weak, some resistance	complete, without resistance	incomplete
Swallowing 4 oz. water (½ cup)	normal	Minimal coughing or throat clearing	severe coughing/choking or nasal regurgitation	cannot swallow (test not attempted)
Speech following 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° sitting)	240	90–239	10–89	0–9
Left arm outstretched (90° sitting)	240	90–239	10–89	0–9
Vital capacity (% predicted)	≥80%	65–79%	50–64%	<50%
Right hand grip (kg)				
male	≥45	15–44	5–14	0–4
female	≥30	10–29	5–9	0–4
Left hand grip (kg)				
male	≥35	15–34	5–14	0–4
female	≥25	10–24	5–9	0–4
Head lifted (45° supine)	120	30–119	1–29	0
Right leg outstretched (45° supine)	100	31–99	1–30	0
Left leg outstretched (45° supine)	100	31–99	1–30	0

Source: ([Barohn et al. 1998](#)).

Abbreviations: QMG, quantitative myasthenia gravis

Reviewer's Comments: *The Division previously agreed with the acceptability of the change from baseline on QMG scale as a key secondary endpoint. There is also regulatory precedent for the use of the QMG as a clinical endpoint for gMG, as it was also used in the clinical studies that led to the approval of eculizumab, ravulizumab, and efgartigimod for gMG. Although the QMG assesses exam findings of gMG that may be of uncertain clinical meaningfulness, it supports that changes observed on the MG-ADL are related to improvements in physical manifestations of the disease.*

The Myasthenia Gravis Composite (MG-C) is a 10-item subject-reported and physician assessment scoring system ([Table 10](#)). The MG-C is composed of items originating from other scales (i.e., QMG, manual muscle testing, MG-ADL). Items are related to ptosis, double vision, eye closure, talking, chewing, swallowing, breathing, neck flexion, shoulder abduction, and hip flexion. Each item is scored on an ordinal scale with four possible categories and weighted. The total score ranges from 0 to 50, with higher scores indicating more severe impairments.

Table 10. Myasthenia Gravis Composite Scale
MG composite scale

Ptosis, upward ease (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 2	Immediate = 3
Double vision on lateral Gaze, left or right (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eye closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, for example necessitating change in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, $\pm 15\%$) = 3	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, $\pm 15\%$) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, $\pm 15\%$) = 4	Severe weakness = 5
TOTAL				

Note: Please note that “moderate weakness” for neck and limb items should be construed as weakness that equals roughly $50\% \pm 15\%$ of expected normal strength. Any weakness milder than that would be “mild,” and any weakness more severe than that would be classified as “severe.”

Source: (Burns et al. 2010).

Abbreviations: MG, myasthenia gravis

Reviewer’s Comments: (b) (4)

The MG-C contains items which overlap with MG-ADL and QMG and (b) (4)

Myasthenia Gravis Symptoms PRO (MGSPRO)

The MG Symptoms PRO (MGSPRO; Table 11) is a 42-item PRO instrument measuring five symptom concepts of MG including ocular muscle weakness (5 items), bulbar muscle weakness (10 items), respiratory muscle weakness (3 items), physical fatigue (15 items), and muscle weakness fatigability (9 items). The MGSPRO instrument was developed based on interviews with 96 subjects with MG and quantitative psychometric analysis of data from a total of 273 subjects with MG (30 from the qualitative research sample, 43 from the phase 2 study, MG0002, and 200 from MG0003). The Applicant has included change from baseline to day 43 in three MGSPRO domains in the Study MG0003: muscle weakness fatigability, physical fatigue, and bulbar muscle weakness as secondary efficacy endpoints.

The MGSPRO was administered weekly with a recall period of 7 days for each item during the double-blind treatment period. The MG0003 study endpoints were defined using the MG Symptoms PRO scale scores which are simple linear transformation of the raw score on a 0 to 100 range. The item-level raw scores were summed first and the raw total score subsequently transformed to 0 to 100. A scale score was calculated if more than 70% of items were responded to minimize missing items data. In Study MG0003, 1307 out of 1329 assessments (98.3%) were considered completed, nine (0.7%) included one missing item, whereas 7 (0.5%) had full questionnaire missing. The missing data were observed across a variety of items of the MGSPRO instrument.

The Applicant provided anchor based empirical cumulative distribution function and probability distribution function for a patient global impression of severity scale (PGI-S) and global impression of change scale, as per the Division's recommendations in the Type B end-of-phase 2 meeting on May 22, 2019.

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Comments: *Previously, the Division of Neurology 1 (DN1) and the Clinical Outcome Assessment review team provided recommendations regarding MGSPRO in the pre-IND meeting minutes dated December 9, 2016, Type B end-of-phase 2 meeting minutes dated June 14, 2019, and Type C written responses on November 3, 2020 (IND132407). Specifically, DN1 expressed concerns regarding the 7-day recall period, the length of the instrument and concept redundancy which increases burden to subjects and missing data. DN1 recommended that the Applicant conduct exit interviews which may provide an opportunity to obtain a subject's input on what they consider to be a meaningful change. However, the recall period, the instrument redundancy, and the instrument items length were unchanged, and no exit interviews were conducted for the study.*

6.2.2.2. Eligibility Criteria, Study MG0003

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

Inclusion Criteria

To participate in this study, subjects were required to meet the following eligibility criteria:

- Male or female subjects aged ≥ 18 years
- Diagnosis of gMG based on history and previous evaluations
- Positive record of anti-AChR or anti-MuSK autoantibodies at screening (visit 1). The presence of autoantibodies may be confirmed with repeat testing at visit 1.
- Myasthenia Gravis Foundation of America (MGFA) Class II to Iva at visit 1. The MGFA classification is shown in [Figure 2](#).
- A MG-ADL score of at least 3 (with ≥ 3 points from nonocular symptom) AND a QMG score of at least 11 at visit 1 and at baseline (visit 2).
- Being considered for additional treatment such as IVIg or PEX by the investigator.
- Bodyweight ≥ 35 kg at visit 1.
- Highly effective contraception
- Able to give informed consent

Figure 2. Myasthenia Gravis Foundation of America (MGFA) Classification

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.

- A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- B. 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.

- A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- B. 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.

- A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- B. 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
Abbreviations: MGFA, Myasthenia Gravis Foundation of America

Key Exclusion Criteria

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

- Has a severe (defined as grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or who has myasthenic crisis or impending crisis at visit 1 or visit 2.
- Has the following laboratory abnormalities:
 - Serum total IgG level ≤ 5.5 g/L.
 - Absolute neutrophil count < 1500 cells/mm³.
 - Significant electrocardiogram findings as assessed by the investigator.
 - Fridericia corrected QT interval > 450 msec (for male subjects) or corrected QT interval > 470 msec (for female subjects) or corrected QT interval > 480 msec in subjects with bundle branch block.
 - Glomerular filtration rate (GFR) less than 45 mL/min/1.73m² at visit 1.

- Alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) are >3x upper limit of normal (ULN), or bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- Presence of hepatitis B surface antigen at visit 1.
- Positive hepatitis C antibody or ribonucleic acid test result at visit 1 or within 3 months prior to starting study treatment.
- Positive for human immunodeficiency virus.
- Current unstable liver or biliary disease per the investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: with exception of stable hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).
- Has a current or medical history of primary immunodeficiency.
- Has active neoplastic disease or history of neoplastic disease within 5 years of study entry prior to visit 1 (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that have been definitively treated with standard of care approaches).
- Any medical or psychiatric condition that in the opinion of investigator may jeopardize or would compromise the subject's ability to participate in the study.
- A history of alcohol or substance use disorder within 12 months before visit 1.
- A clinically relevant active infection (e.g., sepsis, pneumonia, or abscess) in the opinion of the investigator, or had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of investigational medicinal product.
- A known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection, or current/history of nontuberculous mycobacterial infection.
- Has been treated with prohibited immunosuppressants, biologics, or other therapies (Table 12). Permitted concomitant MG medications are listed in Table 13.
- Have received a live vaccination within 8 weeks prior to visit 2; or intends to have a live vaccination during the course of the study or within 8 weeks following the final dose of investigational medicinal product.
- Has previously received rozanolixizumab drug product.
- Has prior treatment with rituximab in the 6 months prior to visit 2 or study subject has prior treatment with rituximab in the 12 months prior to visit 2 and B cells monitoring have shown they did not return to normal range.
- Had a thymectomy in the past 6 months or a thymoma at any time that required chemotherapy and/or radiotherapy prior to visit 1.
- Has any of the following active GI disorders: inflammatory bowel disease, or GI ulceration or diverticulitis.

- Has experienced hypersensitivity reaction after exposure to other anti-FcRn drugs.
- Has a history of a solid organ transplant or hematopoietic stem cell/marrow transplant

Table 12. Treatment-Free Period for Exclusionary Immunosuppressants, Biologics, and Other Therapies Prior to Baseline (Visit 2)

Generic name (commercial/trade names)	Period relative to Baseline Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide (Cytosan®)	6 months
Pimecrolimus (Elidel®)	4 weeks
Vinca alkaloids (vincristine, vinblastine)	12 weeks
Biologics (Mabs and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	6 months
Eculizumab (Soliris®)	3 months
Belimumab (Benlysta®)	6 months
Golimumab (Simponi®)	6 months
Natalizumab (Tysabri®)	6 months
Ofatumumab (Arzerra)	6 months
Rituximab (Rituxan®)	6 months or 12 months if B-cells did not return to normal range
Ocrelizumab (Ocrevus®)	6 months or 12 months if B-cells did not return to normal range
TACI-Ig (Atacicept)	10 months
Veltuzumab	6 months
Other biologics	3 months, or within 5 half-lives (whichever was longer) prior to the Baseline Visit
Inebulizumab	6 months (prior to Baseline Visit) and B-cells are within normal range
Others	
Intravenous or subcutaneous immunoglobulin	4 weeks
IPP-201101 (Lupuzor™)	3 months
PEX	4 weeks
Immunoadsorption	4 weeks

Source: Protocol Study MG0003 dated February 12, 2021, Table 5-1 on Page 41.

Abbreviations: PEX, plasma exchange

Table 13. Permitted Concomitant MG Care Medications, Study MG0003

Permitted Medications	Dose	Comment
Oral Corticosteroids (eg, prednisolone)	No specific requirements	Stable for 4 weeks prior to Baseline ^a
Methotrexate	≤30mg/week	Treated for previous 6 months and on stable dose for 2 months prior to Baseline ^a
Mycophenolate mofetil	≤3g/day	Treated for previous 6 months and on stable dose for 2 months prior to Baseline ^a
Cyclosporine ^b	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)	Treated for previous 6 months and on stable dose for 2 months prior to Baseline ^a
Azathioprine	≤3mg/kg/day	Treated for previous 6 months and on stable dose for 2 months prior to Baseline ^a
Cholinesterase inhibitors	≤600mg Pyridostigmine/day	Stable dose not required – dose held on mornings of efficacy outcomes
Tacrolimus ^c	≤5mg/day	Treated for previous 6 months and on stable dose for 2 months prior to Baseline ^a

^a Must also be stable for duration of study.

^b Doses higher than listed are permissible if trough level is ≤300ng/mL.

^c If the total daily weight-based dose is >5mg, then a plasma trough level should be checked to ensure study participant is not above the recommended therapeutic range.

Source: MG0003 protocol-amend-4
Abbreviations: MG, myasthenia gravis

Compliance With Good Clinical Practice, Study MG0003

Study execution, protocol adherence, and data integrity appear adequate. The data generated are interpretable. Union Chimique Belge (UCB), Inc. attested to good clinical practices such as human subject protection, institutional review board compliance, and clinical investigator obligations including financial disclosures as defined in International Council on Harmonisation-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

6.2.2.3. Statistical Analysis Plan, Study MG0003

The primary efficacy analysis compared rozanolixizumab of ≈7 mg/kg dose and rozanolixizumab of ≈10 mg/kg dose to placebo following a 2-stage group sequential design using a combination test. The final version of the protocol of Study MG0003 was dated

February 23, 2021. The final version of statistical analysis plan (SAP) of Study MG0003 was dated November 10, 2021.

The analysis was conducted on the randomized set, consisting of all study subjects who were randomized. The subjects were analyzed using the treatment assigned instead of the actual treatment received. The familywise type I error rate was controlled at a 2-sided alpha level of 0.05 by using a parallel gatekeeping testing procedure with a truncated Hochberg test.

An IDMC monitored the ongoing safety and efficacy of the study to make recommendations on futility, selection of the “best dose” of rozanolixizumab, and sample size re-estimation. The interim analysis was performed on 92 enrolled study subjects with a data cutoff date of April 13, 2021. The IDMC recommended that the study remained unchanged, with both the ≈ 7 mg/kg and ≈ 10 mg/kg doses carried forward. The recommended sample size for the second stage of the study was 90 subjects (i.e., 30 subjects per treatment group). The primary efficacy analysis of the primary endpoint was conducted with a stagewise mixed model repeated measures (MMRM) using an inverse-normal method of combining independent stagewise p-values. The model included treatment group, baseline MG-ADL score, region, stratification factors including AChR(+/-) and MuSK(+/-), and treatment group by day (interaction term) as fixed factors and study subject as a random effect. The MMRM included days 8, 15, 22, 29, 36 and 43. An unstructured covariance matrix was used for the repeated measures. Missing data were handled under a missing at random assumption using a hypothetical and treatment policy strategy to handle intercurrent events (ICEs). The combined p-value (2-sided) for the two stages was based on the stagewise inverse-normal combination of independent stagewise p-values using the Lehman and Wassmer method. The multiplicity adjusted 95% CIs were provided for the differences in least squares (LS) mean change from baseline in MG-ADL score to day 43 (visit 10) between rozanolixizumab groups and placebo. The lower bound of the 2-sided 95% repeated confidence interval for a given treatment group was found as the smallest value for which the multiplicity-adjusted combination test yields nonrejection at a two-sided alpha =5%. The upper bound of the confidence interval was found analogously.

The key secondary endpoints of change from baseline to day 43 in MG-C score, change from baseline to day 43 in QMG score, and changes from baseline to day 43 in MGSPRO domains muscle weakness fatigability score, physical fatigue score and bulbar symptoms score were analyzed using the same approach as that of the primary analysis of the primary endpoint.

6.2.2.4. Results of Analyses, Study MG0003

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of rozanolixizumab.

6.2.2.4.1. Disposition, Baseline Demographics and Baseline Clinical Characteristics

Disposition

Subject disposition information for the randomized set is summarized in [Table 14](#). The percentage of the total 200 study subjects who completed the study was 64.0% (n=128). Seventy-

two subjects (36.0%) discontinued the study permanently; all discontinuations occurred during the coronavirus disease of 2019 (COVID-19) pandemic. The discontinuation percentages were similar across the 3 treatment groups, 37.3% in placebo group, 34.8% in rozanolixizumab of ≈ 7 mg/kg dose group and 35.8% in rozanolixizumab of ≈ 10 mg/kg dose group. The most common reasons for discontinuation were mandatory withdrawal and roll over to MG0004 and MG0007.

Table 14 Disposition, Study MG0003

Study Status	Placebo N=67	Rozanolixizumab ≈ 7 mg/kg N=66	Rozanolixizumab ≈ 10 mg/kg N=67	Total N=200
End of study status, n (%)				
Completed	42 (62.7)	43 (65.2)	43 (64.2)	128 (64.0)
Discontinued	25 (37.3)	23 (34.8)	24 (35.8)	72 (36.0)
Primary reason for discontinuation, n (%)				
Adverse event	2 (3.0)	2 (3.0)	5 (7.5)	9 (4.5)
Lack of efficacy	5 (7.5)	1 (1.5)	1 (1.5)	7 (3.5)
Lost to Follow-up	0	1 (1.5)	0	1 (<1)
Other, n (%)	18 (26.9)	19 (28.8)	18 (26.9)	55 (27.5)
Due to COVID-19 pandemic	0	1 (1.5)	1 (1.5)	2 (1.0)
Mandatory withdrawal and roll over to MG0004	7 (10.4)	8 (12.1)	6 (9.0)	21 (10.5)
Mandatory withdrawal and roll over to MG0007	10 (14.9)	6 (9.1)	9 (13.4)	25 (12.5)

Source: Statistical Reviewer Analysis; adsl

Abbreviations: COVID-19, coronavirus disease of 2019; MG, myasthenia gravis

Baseline Demographics and Clinical Characteristics

Demographics for the Study MG0003 are described in the following tables, based on the submitted data (Table 15, Table 16, and Table 17). Study MG0003 enrolled 200 subjects, almost all during the COVID-19 pandemic (183 [91.5%]; and the rest (17 [8.5%]) during the pre-COVID-19 pandemic period. One hundred twenty (60.5%) were female. This sex imbalance is consistent with the natural history of the disease, as described in Section 2.1. There were 66 subjects randomized to the rozanolixizumab ≈ 7 mg/kg group, and 67 subjects each to the rozanolixizumab ≈ 10 mg/kg and placebo groups. There was a higher proportion of female study subjects in the placebo group (70.2%) compared with the rozanolixizumab groups (≈ 7 mg/kg [59.1%] and ≈ 10 mg/kg [52.2%]). There were few subjects in the <50 kg body weight category at baseline (6%) and fewer in the ≈ 10 mg/kg dose group compared to the ≈ 7 mg/kg and placebo groups (1.5% versus 10.6% and 6%, respectively). At baseline, age and race were adequately balanced between the placebo and rozanolixizumab groups. Subjects 65 years and older comprised 24.5% of total and were adequately balanced between the treatment arms. The majority (89.5%) of subjects were anti-AChR antibody positive and the remaining 10.5% of subjects were anti-MuSK autoantibody positive. At baseline, the disease severity and the localization of symptoms, as indicated by the Myasthenia Gravis Foundation of America (MGFA) classification, were similar between the subjects randomized to rozanolixizumab or placebo. The subjects had moderate to severe gMG with a larger proportion of the randomized subjects in the MGFA class III and IV (61%), and the rest in the MGFA class II (39%). The MG-

ADL and QMG scores, and disease duration at baseline were balanced between the placebo and rozanolixizumab groups. The mean MG-ADL score was 8.3, the mean QMG score was 15.6, the mean disease duration was 8.6 years, and 29.5% of the randomized subjects had a history of MG crisis in the past. The treatment groups were balanced with regard to standard of care including the use of steroids, nonsteroidal immunosuppressant drugs, and acetylcholine esterase inhibitor drugs. Relatively fewer subjects in the rozanolixizumab ≈ 10 mg/kg group had undergone thymectomy compared with the ≈ 7 mg/kg and placebo groups (29.9% versus 48.5% and 46.3%, respectively). The presence of medical conditions other than gMG was similar between the rozanolixizumab and placebo groups. The most frequent medical comorbidity was systemic hypertension (31.5%). Headaches were reported in only 10% of total subjects with a half of them reporting headaches as migraines at baseline ([Table 17](#))

Reviewer's Comments: Overall, there is an acceptable balance of demographic characteristics between the placebo and rozanolixizumab treatment groups that adequately represents the demographics of the intended subject population with moderate to severe gMG who are seropositive for anti-AChR or anti-MuSK antibodies. The proportion of female subjects and subjects with anti-MuSK antibodies is consistent with the disease prevalence in the intended patient population ([Gilhus et al. 2019](#)). Note that anti-MuSK antibody seropositive subjects were not included in the previous clinical studies that led to approval of eculizumab and ravulizumab in gMG. For efgartgimod, six subjects in the anti-AChR antibody negative group had anti-MuSK antibodies in the study (three in active arm, three in placebo arm); however, efficacy in the anti-MuSK subgroup was not established in that study. A majority (95.5%) of the subjects in Study MG003 were on concomitant medications including, acetylcholine esterase inhibitor drugs, steroids, and nonsteroidal immunosuppressant drugs with balanced distribution across treatment groups.

Protocol Deviations, Study MG0003

No subjects were excluded from any analysis due to protocol deviation. A total of 22 subjects (11%; 21 during the COVID-19 pandemic [10.5%]) had an important protocol deviation including, procedural noncompliance (n=8 [4%]), inclusion criteria deviation and incorrect treatment dose (n=4 [2%] each), withdrawal criteria deviation and prohibited concomitant medication use (n=3 [1.5%] each), and exclusion criteria deviation (n=2 [1%]).

Reviewer's Comments: The protocol deviations affected 11% of the randomized subjects and none were excluded from any analysis. They were unlikely to have had an impact on the efficacy and safety analyses.

Impact of the COVID-19 Pandemic on Study MG0003

A majority of the subjects enrolled (91.5%) were randomized during the COVID-19 pandemic (the first laboratory-confirmed case of COVID-19 in the United States was January 20, 2020; the WHO declared a pandemic on March 11, 2020). The recruitment was paused due to the pandemic from March 20, 2020, to June 3, 2020, but the randomized subjects continued the study. The pandemic impacted 13 subjects (6.5%) and a total of 33 visits including, 12 visits due to confirmed COVID-19 infection (n=6 visits not done, n=4 visits noted as temporary discontinuation of study drug, and n=2 visits performed by telephone).

Reviewer's Comments: The impact of the COVID-19 pandemic was minor and affected a relatively small number of the subjects. There were no protocol deviations related to COVID-19. The first subject was randomized (b) (6), and the last study drug infusion was (b) (6), with the final study visit (b) (6). The interim analysis was April 13, 2021, of 92 subjects who had completed the 6-week treatment period.

Table 15. Baseline Demographics and Clinical Characteristics, Safety Population, Study MG0003

Characteristic	Placebo (N=67)	Rozanolixizumab ≈7 mg/kg (N=66)	Rozanolixizumab ≈10 mg/kg (N=67)	All (N=200)
Sex, n (%)				
Female	47 (70.2)	39 (59.1)	35 (52.2)	121 (60.5)
Male	20 (29.8)	27 (40.9)	32 (47.8)	79 (39.5)
Age, years				
18 to <65	51 (76.1)	49 (74.2)	51 (76.1)	151 (75.5)
≥65	16 (23.9)	17 (25.8)	16 (23.9)	49 (24.5)
Ethnicity, n (%)				
Hispanic or Latino	5 (7.5)	5 (7.6)	3 (4.5)	13 (6.5)
Non-Hispanic or Latino	48 (71.6)	47 (71.2)	58 (86.6)	153 (76.5)
Missing	0	0	0	0
Not reported	14 (20.9)	14 (21.2)	6 (8.9)	34 (17.0)
Race, n (%)				
American Indian or Alaska Native	1 (1.5)	0	0	1 (1.5)
Asian	5 (7.5)	9 (13.7)	7 (10.5)	21 (10.5)
Black or African American	1 (1.5)	0	4 (6.0)	5 (2.5)
White	46 (68.6)	41 (62.1)	49 (73.0)	136 (68.0)
Multiple	0	0	0	0
Not reported	14 (20.9)	16 (24.2)	7 (10.5)	37 (18.5)
Region				
Japan	4 (6.0)	5 (7.6)	4 (6.0)	13 (6.5)
United States	16 (23.9)	11 (16.7)	14 (20.9)	41 (20.5)
Rest of the world	47 (70.1)	50 (75.7)	49 (73.1)	146 (73.0)
Weight, Kg				
Mean (SD)	80.8 (22.6)	79.5 (25.5)	83.1 (23.7)	81.1 (23.9)
Median (min, max)	80 (39.7 to 150.5)	78 (37.7 to 154.2)	76.6 (46.9 to 155.6)	78.0 (37.7 to 155.6)
<50 Kg, n (%)	4 (6.0)	7 (10.6)	1 (1.5)	12 (6.0)
50 to <70 Kg, n (%)	16 (23.9)	19 (28.8)	26 (38.8)	61 (30.5)
70 to 100 Kg, n (%)	35 (52.2)	26 (39.4)	22 (32.8)	83 (41.5)
>100 Kg, n (%)	12 (17.9)	14 (21.2)	18 (26.9)	44 (22.0)
BMI, (kg/m ²)				
Mean (SD)	28.0 (6.2)	27.4 (6.9)	28.1 (6.3)	27.8 (6.4)
Median (min, max)	28.1 (13.7 to 41.7)	26.4 (14.2 to 47.6)	27.0 (15.3 to 45.5)	27.2 (13.7 to 47.6)

Source: adsl.xpt

Abbreviations: BMI, body mass index

Table 16. Other Baseline Characteristics Including Baseline Concomitant Medications. Study MG0003

Characteristic	Placebo (N=67)	Rozanolixizumab ≈7 mg/kg (N=66)	Rozanolixizumab ≈10 mg/kg (N=67)	All (N=200)
MGFA disease class at baseline, n (%)				
Class Iia	11 (16.4)	13 (19.7)	13 (19.4)	37 (18.5)
Class Iib	12 (17.9)	16 (24.2)	13 (19.4)	41 (20.5)
Class IIIa	28 (41.8)	21 (31.8)	26 (38.8)	75 (37.5)
Class IIIb	13 (19.4)	13 (19.7)	13 (19.4)	39 (19.5)
Class Iva	2 (3.0)	3 (4.5)	2 (3.0)	7 (3.5)
Class Ivb	1 (1.5)	0	0	1 (0.5)
Thymectomy, n (%)	31 (46.3)	32 (48.5)	20 (29.9)	83 (41.5)
MG-ADL score				
Mean (SD)	8.4 (3.4)	8.4 (3.8)	8.1 (2.9)	8.3 (3.4)
Median (min, max)	8.0 (3.0 to 16.0)	8.0 (3.0 to 18.0)	8.0 (3.0 to 16.0)	8.0 (3.0 to 18.0)
Score ≥5, n (%)	57 (85.1)	55 (83.3)	61 (91.0)	173 (86.5)
QMG score				
Mean (SD)	15.8 (3.5)	15.4 (3.7)	15.6 (3.7)	15.6 (3.6)
Median (min, max)	15.0 (11.0 to 23.0)	15.0 (9.0 to 27.0)	15.0 (11.0 to 27.0)	15.0 (9.0 to 27.0)
Myasthenia crisis in the past, n (%)				
Yes	23 (34.3)	19 (28.8)	17 (25.4)	59 (29.5)
No	44 (65.7)	46 (69.7)	49 (73.1)	139 (69.5)
Missing	0	1 (1.5)	1 (1.5)	2 (1.0)
Duration of disease (years)				
Mean (SD)	9.4 (9.3)	6.9 (6.8)	9.6 (9.9)	8.6 (8.8)
Median (min, max)	6.8 (0.1 to 48.9)	5.3 (0.1 to 33.1)	5.7 (0.2 to 46.4)	5.8 (0.1 to 48.9)
Age at initial MG diagnosis (years)				
Mean (SD)	41.4 (19.1)	46.6 (16.0)	42.6 (19.1)	43.5 (18.2)
Median (min, max)	38.0 (12.0 to 79.0)	46.0 (13.0 to 83.0)	40.0 (11.0 to 76.0)	44.0 (11.0 to 83.0)
Historical ¹ MG-specific autoantibody, n (%)				
Anti-AChR positive	59 (88.1)	60 (90.9)	60 (89.6)	179 (89.5)
Anti-MuSK positive	8 (11.9)	5 (7.6)	8 (11.9)	21 (10.5)
Anti-AChR and Anti-MuSK positive	1 (1.5)	0	1 (1.5)	2 (1.0)
Anti-MuSK positive and Anti-AChR negative ²	5 (7.5)	3 (4.5)	5 (7.5)	13 (6.5)
Anti-AChR positive and Anti-MuSK negative ³	17 (25.4)	14 (21.2)	17 (25.4)	48 (24.0)
Seronegative for anti-AChR and anti-MuSK	0	0	0	0

Characteristic	Placebo (N=67)	Rozanolixizumab ≈7 mg/kg (N=66)	Rozanolixizumab ≈10 mg/kg (N=67)	All (N=200)
Baseline ⁴ MG-specific autoantibody status, n (%)				
Anti-AChR positive	53 (79.1)	56 (84.8)	56 (83.6)	165 (82.5)
Anti-MuSK positive	8 (11.9)	4 (6.1)	4 (6.0)	16 (8.0)
Anti-AChR and Anti-MuSK positive	1 (1.5)	0	0	1 (0.5)
Anti-MuSK positive and Anti-AChR negative ²	7 (10.4)	4 (6.1)	4 (6.0)	15 (7.5)
Anti-AChR positive and Anti-MuSK negative ³	52 (77.6)	56 (84.8)	56 (83.6)	164 (82.0)
Seronegative for anti-AChR and anti-MuSK	4 (6.0)	1 (1.5)	3 (4.5)	8 (4.0)
Standard of care, n (%)				
Any AChE inhibitor	60 (89.6)	55 (83.3)	57 (85.1)	172 (86.0)
Any NSIDs	33 (49.3)	32 (48.5)	38 (56.7)	103 (51.5)
Any steroid	38 (56.7)	43 (65.2)	48 (71.6)	129 (64.5)
Both/combination corticosteroid and NSID	21 (31.3)	24 (36.4)	26 (38.8)	71 (35.5)
Either steroid or NSID	28 (41.8)	25 (37.9)	33 (49.3)	86 (43.0)
No concomitant medications (AChE inhibitor, steroid or NSID)	3 (4.5)	3 (4.5)	3 (4.5)	9 (4.5)
NSIDs, n (%)				
Azathioprine	19 (28.4)	17 (25.8)	20 (29.9)	56 (28.0)
Mycophenolate mofetil/mycophenolic acid	7 (10.4)	9 (13.6)	6 (9.0)	22 (11.0)
Tacrolimus	4 (6.0)	4 (6.1)	6 (9.0)	14 (7.0)
Cyclosporin	3 (4.5)	2 (3.0)	4 (6.0)	9 (4.5)
Methotrexate	0	0	2 (3.0)	2 (1.0)
Leflunomide	0	1 (1.5)	0	1 (0.5)

Source: Module 2.7.3 Summary of Clinical Efficacy Table 2 – 1 on page 28 dated Oct 18, 2022; Module 2.7.4. Summary of Clinical Safety Table 1 – 15 on page 51 dated 29-Sep-2022; Module 5.3.5.1, MG0003, gmg-rozi-tables-fda-ir4-response-20230113; Derived from MG0003 CSR Table 3.1.3. and Table 5.3.1.

¹Historical records of MG-specific autoantibody seropositivity; ²Anti-AChR unknown not included; ³Anti-MuSK unknown not included; ⁴antibody tests done at baseline visit

Abbreviations: AChE, acetylcholine esterase; AChR, acetylcholine receptor; MG-ADL, myasthenia gravis activities of daily living; MG-ADL, Myasthenia Gravis-Specific Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; NSID, nonsteroidal immunosuppressive drug; NSID, nonsteroidal immunosuppressive drug; QMG, Quantitative Myasthenia Gravis; QMG, quantitative myasthenia gravis Abbreviations: AChE, acetylcholinesterase

Table 17. Previous and Ongoing Medical Conditions Other Than MG That Occurred Before Study Entry (by Preferred Term, Frequency >5% in Total Study Population)

Parameter	Placebo (N=67) n (%)	Rozanolixizumab ≈7 mg/kg (N=66) n (%)	Rozanolixizumab ≈10 mg/kg (N=67) n (%)	All (N=200) n (%)
Hypertension	21 (31.3)	22 (33.3)	20 (29.9)	63 (31.5)
Psychiatric disorders	10 (14.9)	16 (24.2)	15 (22.4)	41 (20.5)
Depression ¹	5 (7.5)	9 (13.6)	7 (10.4)	21 (10.5)
Renal and urinary disorders	10 (14.9)	10 (15.2)	13 (19.4)	33 (16.5)
Hypothyroidism	10 (14.9)	8 (12.1)	8 (11.9)	26 (13.0)
Cataract	8 (11.9)	9 (13.6)	5 (7.5)	22 (11.0)
Osteoporosis	6 (9.0)	6 (9.1)	9 (13.4)	21 (10.5)
Breathing abnormalities	5 (7.5)	7 (10.6)	8 (11.9)	20 (10.0)
Sleep apnea	5 (7.5)	5 (7.6)	6 (9.0)	16 (8.0)
Dyspnea	0	2 (3.0)	2 (3.0)	4 (2.0)
Headache	7 (10.4)	6 (9.1)	7 (10.4)	20 (10%)
Migraine	3 (4.5)	3 (4.5)	5 (7.5)	11 (5.5)
Gastroesophageal reflux disease	2 (3.0)	11 (16.7)	7 (10.4)	20 (10%)
Diabetes mellitus type 2	5 (7.5)	7 (10.6)	8 (11.9)	20 (10%)
Thymectomy	7 (10.4)	5 (7.6)	5 (7.5)	17 (8.5)
Injury, poisoning and procedural complications	5 (7.5)	5 (7.6)	7 (10.4)	17 (8.5)
Obesity	5 (7.5)	4 (6.1)	6 (9.0)	15 (7.5)
Supraventricular arrhythmia	7 (10.4)	4 (6.1)	3 (4.5)	14 (7.0)
Insomnia	3 (4.5)	7 (10.6)	3 (4.5)	13 (6.5)
Asthma	2 (3.0)	6 (9.1)	5 (7.5)	13 (6.5)
Thymoma	4 (6.0)	5 (7.6)	3 (4.5)	12 (6.0)
Drug hypersensitivity	3 (4.5)	5 (7.6)	4 (6.0)	12 (6.0)
Hyperlipidemia	4 (6.0)	4 (6.1)	4 (6.0)	12 (6.0)
Osteoarthritis	1 (1.5)	6 (9.1)	5 (7.5)	12 (6.0)
Benign prostatic hyperplasia	3 (4.5)	7 (10.6)	2 (3.0)	12 (6.0)
Upper respiratory tract infections	2 (3.0)	6 (9.1)	3 (4.5)	11 (5.5)
Peripheral neuropathies	4 (6.0)	3 (4.5)	4 (6.0)	11 (5.5)

Source: Derived from MG0003 CSR Table 4.1.1.1

¹includes major depression and mixed anxiety and depressive disorder

6.2.2.4.2. Primary and Key Secondary Efficacy Results

Primary Efficacy Endpoint

The Applicant's primary efficacy results were confirmed by the statistical reviewer. The results demonstrated superiority of rozanolixizumab of ≈7 mg/kg dose level and rozanolixizumab of ≈10 mg/kg dose level compared to placebo in improvement from baseline in MG-ADL score to day 43 in study subjects with gMG.

The difference in least squares (LS) mean change from baseline in MG-ADL score between rozanolixizumab of ≈7 mg/kg dose level group and placebo group was -2.59 (95% CI: -4.09, -1.25; p<0.001) in favor of rozanolixizumab.

The difference in least squares (LS) mean change from baseline in MG-ADL score between rozanolixizumab of ≈10 mg/kg dose level group and placebo group was -2.62 (95% CI: -3.99, -1.16; p<0.001) in favor of rozanolixizumab.

All results in [Table 18](#) below were from the combined MMRM, except Cis and p-values, which were based on the stagewise inverse-normal combination using the Lehman and Wassmer method.

Table 18 Primary Efficacy Analysis: MG-ADL Change From Baseline to Day 43 (Visit 10)

Analysis	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
Missing, n (%)	5 (7)	1 (2)	2 (3)
Change from baseline, LS mean (SE)	-0.78 (0.49)	-3.37 (0.49)	-3.40 (0.49)
Difference from placebo (95% CI)	-	-2.59 (-4.09, -1.25)	-2.62 (-3.99, -1.16)
p-value	-	<0.001	<0.001

Source: Statistical Reviewer Analysis; admgadl

All results are from the combined MMRM, except Cis and p-values, which are based on stagewise inverse normal combination using the Lehman and Wassmer method

Abbreviations: LS, least squares; MG-ADL, myasthenia gravis activities of daily living; MMRM, mixed model repeated measures

The following sensitivity analyses were repeated for the primary endpoint:

- Sensitivity Analysis #1: the full analysis set (FAS) using the hypothetical and treatment policy strategy to handle intercurrent events (ICEs)
- Sensitivity Analysis #2: the randomized set using a jump-to-reference approach for imputation of missing data and using the hypothetical and treatment policy strategy to handle ICEs
- Sensitivity Analysis #3: the subgroup of the randomized set who received all 6 subcutaneous doses using hypothetical and treatment policy strategy to handle ICEs
- Sensitivity Analysis #4: the subgroup of the FAS excluding confirmed COVID-19 cases, using treatment policy strategy to handle ICEs.

The following supplementary analyses were repeated for the primary endpoint:

- Supplementary Analysis #1: the randomized set using the composite strategy to handle the occurrence of an intercurrent event as treatment failures and using a trimmed mean approach to impute missing data
- Supplementary Analysis #2: the randomized set using the treatment policy strategy to handle ICEs.

Results of sensitivity analyses and supplementary analyses are in [Table 19](#). The results of the prespecified sensitivity analyses and supplementary analyses were consistent with the primary analysis results.

Table 19 Summary of Sensitivity and Supplementary Analyses of MG-ADL Change From Baseline to Day 43 (Visit 10)

Analysis	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg
Sensitivity #1			
Missing, n/N (%)	5/67 (7)	1/66 (2)	2/67 (3)
Change from baseline, LS mean (SE)	-0.78 (0.49)	-3.37 (0.49)	-3.40 (0.49)
Difference from placebo (95% CI)	-	-2.59 (-4.09, -1.25)	-2.62 (-3.99, -1.16)
p-value	-	<0.001	<0.001
Sensitivity #2			
Missing, n/N (%)	5/67 (7)	1/66 (2)	2/67 (3)
Change from baseline, LS mean (SE)	-0.79 (0.49)	-3.33 (0.49)	-3.39 (0.50)
Difference from placebo (97.5% CI)	-	-2.54 (-3.62, -1.46)	-2.59 (-3.67, -1.52)
p-value	-	<0.001	<0.001
Sensitivity #3			
Missing, n/N (%)	1/56 (2)	0/56 (0)	1/48 (2)
Change from baseline, LS mean (SE)	-1.00 (0.50)	-3.01 (0.49)	-3.02 (0.54)
Difference from placebo (95% CI)	-	-2.01 (-3.51, -0.56)	-2.02 (-3.55, -0.50)
p-value	-	0.003	0.003
Sensitivity #4			
Missing, n/N (%)	3/64 (5)	1/65 (2)	2/66 (3)
Change from baseline, LS mean (SE)	-0.83 (0.49)	-3.38 (0.49)	-3.42 (0.50)
Difference from placebo (95% CI)	-	-2.54 (-4.09, -1.19)	-2.58 (-3.98, -1.09)
p-value	-	<0.001	<0.001
Supplementary #1			
Missing, n/N (%)	5/67 (7)	3/66 (5)	7/67 (10)
Change from baseline, LS mean (SE)	-1.30 (0.59)	-3.87 (0.58)	-4.03 (0.63)
Difference from placebo (97.5% CI)	-	-2.57 (-3.93, -1.21)	-2.73 (-4.10, -1.37)
p-value	-	<0.001	<0.001
Supplementary #2			
Missing, n/N (%)	3/67 (4)	1/66 (2)	2/67 (3)
Change from baseline, LS mean (SE)	-0.90 (0.48)	-3.37 (0.48)	-3.41 (0.49)
Difference from placebo (95% CI)	-	-2.47 (-3.95, -1.16)	-2.51 (-3.86, -1.08)
p-value	-	<0.001	<0.001

Source: Statistical Reviewer Analysis; admgadl
Abbreviations: LS, least squares

Key Secondary Efficacy Endpoints

- Change from baseline to day 43 in MG-C Score and change from baseline to day 43 in QMG score were two key secondary endpoints. The alpha level from the parallel gatekeeping

procedure with a truncated Hochberg test was 0.03 for both of these two key secondary endpoints.

- The difference in LS mean change from baseline in MG-C score between rozanolixizumab of ≈ 7 mg/kg dose level group and placebo group was -3.90 (95% CI: -6.63, -1.25; $p < 0.001$).
- The difference in LS mean change from baseline in MG-C score between rozanolixizumab of ≈ 10 mg/kg dose level group and placebo group was -5.53 (95% CI: -8.30, -2.97; $p < 0.001$). ([Table 20](#))
- The difference in LS mean change from baseline in QMG score between rozanolixizumab of ≈ 7 mg/kg dose level group and placebo group was -3.48 (95% CI: -5.61, -1.58; $p < 0.001$).
- The difference in LS mean change from baseline in QMG score between rozanolixizumab of ≈ 10 mg/kg dose level group and placebo group was -4.76 (95% CI: -6.82, -2.86; $p < 0.001$). ([Table 21](#))

Table 20 Secondary Efficacy Analysis: MG-C Change From Baseline to Day 43 (Visit 10)

	Placebo	Rozanolixizumab ≈ 7 mg/kg	Rozanolixizumab ≈ 10 mg/kg
Analysis	N=67	N=66	N=67
Missing, n (%)	5 (7)	1 (2)	5 (7)
Change from baseline, LS mean (SE)	-2.03 (0.92)	-5.93 (0.92)	-7.55 (0.93)
Difference from placebo (95% CI)	-	-3.90 (-6.63, -1.25)	-5.53 (-8.30, -2.97)
p-value	-	<0.001	<0.001

Source: Statistical Reviewer Analysis; admgcs

All results are from the combined MMRM, except Cis and p-values, which are based on stagewise inverse normal combination using the Lehman and Wassmer method.

Abbreviations: LS, least squares; MG-C, myasthenia gravis composite combination using the Lehman and Wassmer method

Table 21. Secondary Efficacy Analysis: QMG Change From Baseline to Day 43 (Visit 10)

	Placebo	Rozanolixizumab ≈ 7 mg/kg	Rozanolixizumab ≈ 10 mg/kg
Analysis	N=67	N=66	N=67
Missing, n (%)	5 (7)	1 (2)	5 (7)
Change from baseline, LS mean (SE)	-1.92 (0.68)	-5.40 (0.68)	-6.67 (0.69)
Difference from placebo (95% CI)	-	-3.48 (-5.61, -1.58)	-4.76 (-6.82, -2.86)
p-value	-	<0.001	<0.001

Source: Statistical Reviewer Analysis; adqmg

All results are from the combined MMRM, except Cis and p-values, which are based on stagewise inverse normal combination using the Lehman and Wassmer method.

Abbreviations: LS, least squares; MMRM, mixed model repeated measures; QMG, quantitative myasthenia gravis

Other Secondary Efficacy Endpoints:

[Table 22](#) shows statistically significant improvement in subjects treated with rozanolixizumab compared with placebo in the secondary efficacy outcomes of change from baseline at day 43 in the MGSPRO domains “muscle weakness fatigability”, “physical fatigue”, and “bulbar muscle weakness” scores in Study MG0003 ($p \leq 0.01$). The Applicant states that considering a 1-point and a 2-point improvement in PGI-S of MG symptoms, a decrease of 16.67 points or more in the muscle weakness fatigability scale, a decrease of 20 points or more in the physical fatigue scale, and a decrease of 20 points or more in the bulbar muscle weakness scale suggested within-

subject clinically meaningful improvement (Module 5.3.5.3; MG-PRO Dossier-FDA). Changes in the muscle weakness fatigability score and physical fatigue, but not bulbar muscle weakness, in subjects treated with rozanolixizumab were 20 points or more.

Table 22. Secondary Efficacy Analysis: MGSPRO Domain Score Change From Baseline to Day 43 (Visit 10)

Analysis	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
MGSPRO domain "Muscle Weakness Fatigability"			
Missing, n (%)	5 (7)	1 (2)	5 (7)
Change from baseline, LS mean (SE)	-10.59 (3.03)	-23.03 (3.03)	-25.75 (3.10)
Difference from placebo (95% CI)	-	-12.44 (-21.80, -4.09)	-15.16 (-23.60, -6.45)
p-value	-	<0.001	<0.001
MGSPRO domain "Physical Fatigue"			
Missing, n (%)	5 (7.5)	1 (1.5)	5 (7.5)
Change from baseline, LS mean (SE)	-10.64 (3.05)	-19.29 (3.05)	-25.46 (3.11)
Difference from placebo (95% CI)	-	-8.65	-14.82
p-value	-	0.012	<0.001
MGSPRO domain "Bulbar Muscle Weakness"			
Missing, n (%)	5 (7.5)	1 (1.5)	5 (7.5)
Change from baseline, LS mean (SE)	-3.52 (2.40)	-14.84 (2.41)	-14.22 (2.46)
Difference from placebo (95% CI)	-	-11.32 (-18.96, -5.0)	-10.71 (-17.79, -4.0)
p-value	-	<0.001	<0.001

Source: MG0003 CSR

All results are from the combined MMRM, except Cis and p-values which are based on stagewise inverse normal combination using the Lehman and Wassmer method.

Abbreviations: LS, least squares; MGSPRO, myasthenia gravis symptoms PRO; MMRM, mixed model repeated measures; QMG, quantitative myasthenia gravis

Reviewer's Comments: In Study MG0003, the Applicant enrolled adult gMG subjects who were primarily anti-AChR antibody positive (89.5%). A smaller number of subjects were anti-MuSK antibody positive (10.5%; 8% based on repeat testing at the baseline visit). The primary endpoint, change from baseline in MG-ADL score to day 43, and the key secondary endpoints, change from baseline to day 43 in MG-C and QMG scores were evaluated in the overall study population that combined both anti-AChR and anti-MuSK antibody positive gMG subjects. The analysis of the overall study population showed a statistically significant difference favoring rozanolixizumab at ≈7 mg/kg and ≈10 mg/kg doses in the mean change from baseline to day 43 in the MG-ADL total scores (-3.4 points in the rozanolixizumab treated groups compared with -0.8 in the placebo group, $p < 0.001$). A statistically significant difference favoring rozanolixizumab was also observed in the mean change from baseline to day 43 in the QMG and MG-C scores ($p < 0.001$). The subjects receiving rozanolixizumab had a greater than 5-point improvement in the MG-C score and QMG score over the same period.

In MG0003 study, a clinical response was defined by the Applicant in the MG-ADL total score as at least a 2-point improvement, and in the QMG and the MG-C total scores as at least a 3-point improvement. The proportion of clinical responders was numerically higher for rozanolixizumab compared to the placebo for the change in the MG-ADL total score at day 43 from the baseline (68.2% and 61.2% in the ≈7 mg/kg and ≈10 mg/kg treatment groups compared with 28.4% in the placebo group, $p < 0.001$) and the odds ratios (95% CI) were 5.8 (2.1, 14.9) and 4.3 (1.6, 11.8) for the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively.

Clinical improvement in the MG-ADL total score was seen as early as day 8 (first postbaseline assessment) in the rozanolixizumab treatment groups compared to the placebo group and the median time to first MG-ADL response was estimated at 16 days and 22 days in the ≈ 7 mg/kg and ≈ 10 mg/kg treatment groups (Figure 3). A similar pattern of clinical response was seen in the favor of rozanolixizumab in the QMG score and the MG-C score during the same treatment period.

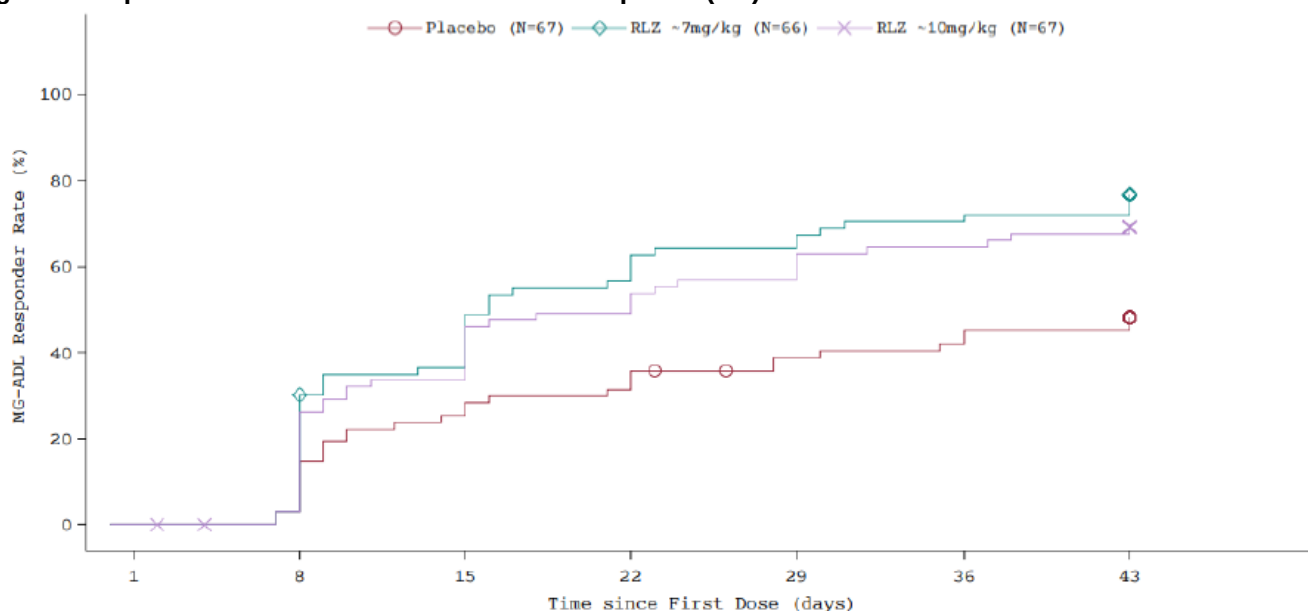
Changes in the secondary endpoints of MGSPRO domain scores support the overall primary and key secondary endpoint responses favoring rozanolixizumab in Study MG0003, indicating clinical benefit of rozanolixizumab that was perceived by subjects with gMG as meaningfully impacting their daily life. In the pre-IND meeting minutes dated December 9, 2016, the Type B end-of-phase 2 meeting minutes dated June 14, 2019, and the Type C written responses dated November 3, 2020 (IND132407), the Division of Neurology 1 (DN1) asked the Applicant to make additional edits to MGSPRO including items reduction, removal of redundant and overlapping items, and reducing the length of the item and recall period to optimize the PRO. The DN1 recommended that the Applicant conduct exit interviews which may provide an opportunity to obtain a subject's input on what they consider to be a meaningful change. However, the recall period, the instrument item redundancy, and the instrument items length were unchanged, and no exit interviews were conducted for the phase 3 study. (b) (4), additional work is needed for MGSPRO to be fit-for-purpose including optimizing the length of the instrument, reducing the concepts overlap with those assessed by other scales (MG-ADL and MG-C), determining the content validity at the item-level, and obtaining patient's input by exit interviews among others. The reviewer notes that with further edits and additional analyses, this instrument may become fit-for-purpose and be useful to support a secondary endpoint in future studies of gMG.

None of the subjects on rozanolixizumab required rescue therapy, whereas three subjects (4.5%) in the placebo group needed rescue therapy (IVIg) during the treatment period. One of these subjects also needed IVIg therapy during the observation period. Three subjects in the rozanolixizumab treatment groups received IVIg during the observation period including two in the ≈ 10 mg/kg group and one in the ≈ 7 mg/kg group 24, 41, and 37 days after the last infusion, respectively.

Note that a large majority (n=180 out of 191; 94.2%) of the subjects who were on concomitant medications including steroids, nonsteroidal immunosuppressant drugs, and acetylcholine esterase inhibitor drugs at baseline visit did not require any changes in the dose, frequency, addition, or removal for the MG standard care during the double-blind treatment period. Three subjects receiving the placebo infusions required addition of a concomitant drug in the same time period (Table 23).

These results indicate an improvement in the activities of daily living, motor function, and disease severity in a greater number of subjects treated with rozanolixizumab compared to those treated with placebo, supporting the clinical efficacy of rozanolixizumab.

Figure 3. Kaplan-Meier Plot of Time to MG-ADL Response (RS)



~≈approximate dose, MG-ADL=Myasthenia Gravis Activities of Daily Living, RLZ=rozanolixizumab, RS=randomized set; TEAE=treatment-emergent adverse event

Notes: MG-ADL response is defined as ≥ 2 -point improvement (decrease) from Baseline.

Study participants who used rescue therapy prior to Day 43 or who were withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response were censored at time of event. Study participants who never achieved a response by Day 43 were censored at the date of their last MG-ADL assessment.

Source: Module 2.7.3 Summary of Clinical Efficacy dated October 18, 2022 Section 2.1.5.2.4 page 40

Table 23. Concomitant Medication(s) Added or Changed During the Double-Blind Treatment Period in Study MG0003 (Randomized Set)

Characteristic	Placebo (N=67) n (%)	Rozanolixizumab ≈7 mg/kg (N=66) n (%)	Rozanolixizumab ≈10 mg/kg (N=67) n (%)	All (N=200) n (%)
AchE inhibitor added	1 (1.5)	0	0	1 (1.5)
AchE inhibitor dose increased	0	0	0	0
Corticosteroid added	0	0	0	0
Corticosteroid dose increased	0	0	0	0
NSID added	1 (1.5)	0	0	1 (1.5)
NSID dose increased	0	0	0	0
Multiple concomitant medications added	1 (1.5)	0	0	1 (1.5)
No change in concomitant medication(s) ¹	60 (89.6)	60 (90.9)	60 (89.6)	180 (90.0)

Source: Module 5.3.5.1, MG0003, gmg-rozi-tables-fda-ir4-response-20230113

¹Subjects who have no concomitant medications are not included. This category includes: no changes in dose, frequency, addition or removal of concomitant medication(s).

Abbreviations: AchE, acetylcholinesterase; NSID, nonsteroidal immunosuppressive drug.

6.2.2.4.3. Subgroup Analyses for the Primary Efficacy Endpoint

Analyses were conducted to assess the treatment effect for subgroups defined by various demographics and clinical characteristics. The subgroup analyses of age, sex, region and weight

to evaluate the efficacy of primary endpoint in [Table 24](#) were generated by the FDA reviewer. To be consistent with the methodologies applied in the primary efficacy analyses of the primary endpoint and the key secondary endpoints, the output's results on subgroups of age, sex and region were from the combined mixed model repeated measures (MMRM) model using an unstructured covariance matrix except for the 95% CIs, which were based on the same method used to produce the multiplicity adjusted 95% CIs for the primary endpoint and key secondary endpoints. The output's results of subgroup analysis of weight including 97.5% CI were from the MMRM model using a covariance matrix of first order autoregressive structure. Of note, the sample size of the subgroup of weight less than 50 kg was small, thus limiting the ability to produce the multiplicity adjusted 95% CIs with the method used for the primary endpoint and limiting the ability to use an MMRM model with an unstructured covariance matrix.

Changes from baseline in MG-ADL score to day 43 of rozanolixizumab of ≈ 7 mg/kg dose level group and rozanolixizumab of ≈ 10 mg/kg dose level group compared to placebo group in study subjects with gMG were generally consistent across subgroups of age, sex, region, and weight.

Table 24. Subgroup Analyses of Primary Endpoint by Age, Sex, Region and Weight, Study MG0003

Demographic Info	Placebo	Rozanolixizumab ≈ 7 mg/kg	Rozanolixizumab ≈ 10 mg/kg
Age (years): 18 to <65 years			
Missing, n/N (%)	4/51 (8)	1/49 (2)	2/51 (4)
Change from baseline, LS mean (SE)	-0.99 (0.53)	-3.57 (0.52)	-3.76 (0.54)
Difference from placebo (95% CI)	-	-2.58 (-4.34, -1.17)	-2.77 (-4.34, -1.18)
Age (years): ≥ 65 years			
Missing, n/N (%)	1/16 (6)	0/17 (0)	0/16 (0)
Change from baseline, LS mean (SE)	0.78 (1.13)	-1.51 (1.26)	-1.08 (1.22)
Difference from placebo (95% CI)	-	-2.29 (-7.26, 0.76)	-1.85 (-5.75, 1.58)
Sex: Female			
Missing, n/N (%)	5/47 (11)	1/39 (3)	1/35 (3)
Change from baseline, LS mean (SE)	-0.89 (0.55)	-3.60 (0.59)	-4.02 (0.59)
Difference from placebo (95% CI)	-	-2.71 (-4.57, -1.17)	-3.13 (-4.99, -1.40)
Sex: Male			
Missing, n/N (%)	0/20 (0)	0/27 (0)	1/32 (3)
Change from baseline, LS mean (SE)	-0.50 (1.04)	-3.12 (0.91)	-2.85 (0.98)
Difference from placebo (95% CI)	-	-2.62 (-5.30, 0.02)	-2.35 (-4.83, 0.20)
Region: United States			
Missing, n/N (%)	3/21 (14)	0/21 (0)	1/18 (6)
Change from baseline, LS mean (SE)	-0.18 (0.77)	-2.33 (0.82)	-2.18 (0.86)
Difference from placebo (95% CI)	-	-2.15 (-4.51, 0.51)	-2.00 (-4.59, 1.03)
Region: Non-United States			
Missing, n/N (%)	2/46 (4)	1/45 (2)	1/49 (2)
Change from Baseline, LS mean (SE)	-0.43 (0.56)	-3.31 (0.58)	-3.32 (0.56)
Difference from placebo (95% CI)	-	-2.88 (-4.66, -1.09)	-2.89 (-4.52, -1.16)

Demographic Info	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg
Weight: <50 kg			
Missing, n/N (%)	0/4 (0)	0/7 (0)	0/1 (0)
Change from baseline, LS mean (SE)	0.52 (1.27)	-0.60 (0.93)	0.51 (1.88)
Difference from placebo (95% CI)	-	-1.12 (-4.24, 2.00)	-0.01 (-5.03, 5.01)
Weight: ≥50 kg to <70 kg			
Missing, n/N (%)	3/16 (19)	0/19 (0)	1/26 (4)
Change from baseline, LS mean (SE)	-0.32 (0.77)	-3.16 (0.68)	-3.35 (0.59)
Difference from placebo (95% CI)	-	-2.84 (-4.85, -0.84)	-3.03 (-4.91, -1.15)
Weight: ≥70 kg to <100 kg			
Missing, n/N (%)	1/35 (3)	0/26 (0)	0/22 (0)
Change from baseline, LS mean (SE)	-0.20 (1.03)	-3.60 (0.99)	-2.85 (1.17)
Difference from placebo (95% CI)	-	-3.40 (-5.22, -1.58)	-2.65 (-4.54, -0.76)
Weight: ≥100 kg			
Missing, n/N (%)	1/12 (8)	1/14 (7)	1/18 (6)
Change from baseline, LS mean (SE)	-1.18 (1.39)	-3.66 (1.46)	-3.95 (1.26)
Difference from placebo (95% CI)	-	-2.48 (-5.07, 0.12)	-2.77 (-5.21, -0.33)

Source: Reviewer generated analysis based on Applicant-submitted data admgadl, adsl.
Abbreviations: LS, least squares

Reviewer Assessment: *There was an improvement (decrease) in MG-ADL score from baseline at day 43 across the subgroups of age, sex, geographical region, and bodyweight in the subjects treated with rozanolixizumab compared to placebo in the phase 3 controlled Study MG0003. Therefore, it appears that rozanolixizumab is effective in both women and men across the range of bodyweight and in different geographical region.*

For age greater than 65, the reviewer notes that it is difficult to adequately determine efficacy in this age group due to small sample size. There were a total of 49 (24.8%) geriatric subjects enrolled in the study. Of these 49 subjects, 46 (93.9%) subjects had anti-AChR-MG and the remaining 3 (6.1%) subjects had anti-MuSK-MG. Only one subject with anti-MuSK-MG was randomized to rozanolixizumab. The reviewer recommends including in the label the following language for geriatric use: “Clinical studies of rozanolixizumab did not include sufficient number of patients aged 65 years and older to determine whether they respond differently from younger adults.”

6.3. Key Efficacy Review Issues

6.3.1. Efficacy in Anti-AChR and Anti-MuSK Antibody Seropositive Myasthenia Gravis

Issue

Evaluate whether the evidence provided by the Applicant supports the proposed indication “Adult (b) (4) with generalized myasthenia gravis who are anti-AChR or anti-MuSK antibody positive”

Background

In the label, the Applicant proposed the following indication, “for the treatment of generalized myasthenia gravis (gMG) in adult (b) (4) who are anti-acetylcholine receptor (AChR) or antimuscle-specific tyrosine kinase (MuSK) antibody positive”.

There are no approved treatments for patients with gMG who are anti-MuSK antibody seropositive (anti-MuSK-gMG). Eculizumab, ravulizumab, and efgartigimod have been approved for the treatment of patients with gMG who are anti-AChR antibody seropositive (anti-AChR-gMG). Steroids and nonsteroidal immunosuppressant drugs (azathioprine, mycophenolate, tacrolimus, methotrexate, and cyclosporine, rituximab) have been used in anti-MuSK gMG patients; however, it is often challenging to achieve a long-term effective remission. About 10 to 15% of patients do not respond to steroids or other immunosuppressant drugs.

Assessment

Baseline Demographics of the Subjects With Anti-MuSK Antibody Positive gMG, Study MG0003

In Study MG0003, randomization into treatment groups was stratified by the presence of MG-specific anti-AChR or anti-MuSK autoantibody. A total of 16 gMG subjects who tested positive for anti-MuSK antibody at baseline were evaluated during the Study MG0003 ([Table 25](#)). This subgroup comprised 8% of total subjects in the study. Of 16 subjects, 8 were assigned to rozanolixizumab treatment arms and 8 were assigned to placebo. One subject in the placebo group also tested positive for AChR antibody. Twelve (75%) subjects were female with balanced distribution between the rozanolixizumab and placebo treatment arms. The subjects had comparable ages and weight-tier distribution at baseline between the groups. There were three subjects (18.7%) who were age 65 years and older. As indicated by the MGFA classification, the subjects had moderate to severe gMG with a larger proportion of the randomized subjects in the MGFA Class III (43.7%) followed by Class II (37.4%), and the rest in the MGFA class IV (18.7%) which reflects the protocol eligibility criteria. All three subjects with severe gMG (MGFA Class IV) were assigned to the placebo group. At baseline, the MG-ADL and QMG scores were balanced between the placebo and rozanolixizumab groups. The mean MG-ADL score was 9.3 (compared to total 200 subjects: 8.3) and the mean QMG score was 15.9 (compared to total 200 subjects: 15.6). The mean disease duration was 11.1 years (compared to total 200 subjects: 8.6 years), and 56.2% (compared to total subjects: 29.5%) of the randomized subjects had a history of MG crisis in the past. Relatively fewer randomized subjects had undergone thymectomy (18.7%). All treatment groups were balanced in regard to standard of care including the use of steroids, nonsteroidal immunosuppressant drugs, and acetylcholine esterase inhibitor drugs.

Reviewer’s Comments: *The subjects with anti-MuSK antibodies comprised 8% of the study subjects based on the testing at baseline visit, which is consistent with the disease prevalence in the intended patient population ([Gilhus et al. 2019](#)). Overall, there appears to be acceptable balance of demographic characteristics between the control and treatment groups that adequately represents the demographics of the intended subject population with moderate to severe gMG who are seropositive for anti-MuSK antibodies. The sex imbalance and the majority of the randomized subjects with the age younger than 65 years are consistent with the natural*

history of the anti-MuSK gMG disease which tends to occur in the 30's with a strong female predominance.

Table 25. Baseline Demographics in the Subjects With Anti-MuSK Antibodies¹, Efficacy Analysis, Study MG0003

Characteristic	Placebo N=8	Rozanolixizumab ≈7 mg/kg N=4	Rozanolixizumab ≈10 mg/kg N=4	All N=16
MG-specific autoantibody, n (%)				
Anti-MuSK positive and anti-AChR negative ¹	7 (87.5)	4 (100)	4 (100)	15 (93.7)
Anti-MuSK positive and anti-AChR-positive ¹	1 (12.5) ^a	0	0	1 (6.2) ^a
Age, years				
Mean (SD)	48.7 (13.4)	48 (8.2)	46.2 (19.9)	47.9 (13.3)
Median (min to max)	44 (36 to 69)	45 (42 to 60)	45.5 (23 to 71)	45 (23 to 71)
19 to <65	6 (75)	4 (100)	3 (75)	13 (81.2)
≥65	2 (25)	0	1 (25)	3 (18.7)
Sex, n (%)				
Female	6 (75)	2 (50)	4 (100)	12 (75)
Male	2 (25)	2 (50)	0	4 (25)
Race, n (%)				
Asian	0	2 (50)	2 (50)	4 (25)
Black or African American	0	0	1 (25)	1 (6.2)
White	8 (100)	2 (50)	1 (25)	11 (68.7)
Ethnic, n (%)				
Hispanic or Latino	1 (12.5)	1 (25)	1 (25)	3 (18.7)
Non-Hispanic or Latino	7 (87.5)	3 (75)	3 (75)	13 (81.2)
Country, n (%)				
Japan	0	1 (25)	2 (50)	3 (18.7)
United States	3 (37.5)	1 (25)	1 (25)	5 (31.2)
Rest of the world	5 (62.5)	2 (50)	1 (25)	8 (50)
Weight, kg				
Mean (SD)	69.6 (22.6)	60.1 (17.5)	72.1 (23.3)	67.9 (20.8)
Median (min to max)	72.6 (39.7 to 103)	61.1 (40.1 to 78)	66.0 (51 to 105.5)	66.0 (39.7 to 105.5)
<50 kg, n (%)	2 (25)	1 (25)	0	3 (18.7)
50 to <70 kg, n (%)	2 (25)	1 (25)	3 (75)	6 (37.5)
70 to <100 kg, n (%)	3 (37.5)	2 (50)	0	5 (31.2)
≥100 kg, n (%)	1 (12.5)	0	1 (25)	2 (12.5)
BMI, kg/m ²				
Mean (SD)	25.1 (7.1)	22.8 (5.5)	26.4 (5.9)	24.8 (6.2)
Median (min to max)	27.6 (13.7 to 32.0)	22.0 (17.2 to 30.1)	25.1 (20.8 to 34.4)	25.1 (13.7 to 34.4)
MGFA Disease Class, n (%)				
Class Iia	1 (12.5)	2 (50)	1 (25)	4 (25)
Class Iib	1 (12.5)	1 (25)	1 (25)	3 (18.7)
Class IIIa	0	0	1 (25)	1 (6.2)
Class IIIb	3 (37.5)	1 (25)	1 (25)	5 (31.2)
Class Iva	2 (25)	0	0	2 (12.5)
Class Ivb	1 (12.5)	0	0	1 (6.2)
MG crisis in the past, n (%)				
Yes	5 (62.5)	2 (50)	2 (50)	9 (56.2)

	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg	All
Characteristic	N=8	N=4	N=4	N=16
No	3 (37.5)	2 (50)	2 (50)	7 (43.7)
Thymectomy, n (%)				
Yes	2 (25)	1 (25)	0	3 (18.7)
No	6 (75)	3 (75)	4 (100)	13 (81.2)
Duration of disease, years				
Mean (SD)	12.2 (7.8) ^b	16 (8.6)	4.3 (4.8)	11.1 (8.2) ^b
Median (min to max)	13.5 (1.8 to 23.7) ^b	19.1 (3.6 to 22.2)	2.6 (0.8 to 11.1)	11.1 (0.8 to 23.7) ^b
MG-ADL score				
Mean (SD)	8.6 (3.85)	10.0 (3.16)	9.8 (3.77)	9.3 (3.49)
Median (min, max)	9.0 (3.0, 14.0)	10.5 (6.0, 13.0)	10.0 (5.0, 14.0)	9.5 (3.0, 14.0)
Score ≥5, n (%)	6 (75.0)	4 (100.0)	4 (100.0)	14 (87.5)
QMG score				
Mean (SD)	17.5 (4.54)	14.5 (1.73)	14.0 (2.71)	15.9 (3.81)
Median (min, max)	19.0 (11.0, 23.0)	14.0 (13.0, 17.0)	13.0 (12.0, 18.0)	14.0 (11.0, 23.0)
Standard of care, n (%)				
Any AchE inhibitor	5 (62.5)	1 (25.0)	2 (50.0)	8 (50.0)
Any NSIDs	5 (62.5)	2 (50.0)	2 (50.0)	9 (56.3)
Any steroid	6 (75.0)	3 (75.0)	4 (100.0)	13 (81.3)
Both/combination				
corticosteroid and NSID	4 (50.0)	2 (50.0)	2 (50.0)	8 (50.0)
Either steroid or NSID	7 (87.5)	3 (75.0)	4 (100.0)	14 (87.5)
No concomitant				
medications (AchE				
inhibitor, steroid or NSID)	1 (12.5)	1 (25.0)	0	2 (12.5)

Source: adsl.xpt

¹adsl.MODEMuSK which according to Module 5.datasets.mg0003 analysis.adam.define.pdf the Applicant had computed as, "Set to BASEMUSK; if BASEMUSK is "Unknown" for randomized subjects, then set to the nonmissing result of earliest postbaseline, if still missing, then set as HISTMUSK (i.e., if stratification factor is MuSK in IWRS, then set to Positive, otherwise set to Negative). (Note: this variable is used for statistical model in efficacy analysis)"

^aHistorical anti-MuSK ant body negative and anti-AChR antibody positive, whereas at baseline seropositive for anti-AChR anti-MuSK antibodies, used in efficacy analysis as anti- MuSK antibody positive

^bTime of symptom onset missing, n=1

Abbreviations: AchE, acetylcholine esterase; AChR, acetylcholine receptor; BMI, body mass index; IWRS, Interactive Web Response System; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; NSID, nonsteroidal immunosuppressive drug; QMG, quantitative myasthenia gravis

The subgroup analyses of MuSK and AChR autoantibody status to evaluate the efficacy of primary endpoint are summarized in [Table 26](#). The results of MuSK and AChR autoantibody status including 97.5% Cis on subgroups were from the MMRM using an unstructured covariance matrix. Of note, the sample sizes of the subgroups of MuSK positive and AChR negative were small, thus limiting the ability to produce the multiplicity adjusted 95% Cis with the method used for the primary efficacy analysis of primary endpoint and key secondary endpoints.

Changes from baseline in MG-ADL score to day 43 of rozanolixizumab of ≈7 mg/kg dose level and rozanolixizumab of ≈10 mg/kg dose level compared to placebo in study subjects with gMG were generally consistent across subgroups of autoantibody status.

Table 26 Summary of Change From Baseline in MG-ADL Score to Day 43 by Autoantibody Status

Change	Placebo (N=67)	Rozanolixizumab ≈7 mg/kg (N=66)	Rozanolixizumab ≈10 mg/kg (N=67)
MuSK Autoantibody: Positive			
Missing, n/N (%)	1/8 (13)	0/4 (0)	0/4 (0)
Change from baseline, LS mean (SE)	-0.04 (1.49)	-6.31 (1.67)	-4.21 (1.80)
Difference from placebo (97.5% CI)	-	-6.27 (-11.41, -1.13)	-4.17 (-9.24, 0.90)
MuSK Autoantibody: Negative			
Missing, n/N (%)	4/59 (7)	1/62 (2)	2/63 (3)
Change from baseline, LS mean (SE)	-0.56 (0.58)	-2.87 (0.58)	-3.05 (0.59)
Difference from placebo (97.5% CI)	-	-2.31 (-3.60, -1.02)	-2.49 (-3.78, -1.21)
AChR Autoantibody: Positive			
Missing, n/N (%)	4/55 (7)	1/60 (2)	2/60 (3)
Change from baseline, LS mean (SE)	-1.36 (1.21)	-3.82 (1.24)	-4.01 (1.25)
Difference from placebo (97.5% CI)	-	-2.46 (-3.80, -1.12)	-2.64 (-3.98, -1.30)
AChR Autoantibody: Negative			
Missing, n/N (%)	1/12 (8)	0/6 (0)	0/7 (0)
Change from baseline, LS mean (SE)	-1.47 (1.03)	-5.43 (1.24)	-4.11 (1.20)
Difference from placebo (97.5% CI)	-	-3.96 (-7.70, -0.22)	-2.64 (-6.18, 0.89)

Source: Statistical Reviewer generated analysis based on Applicant submitted data admgadl, adsl.

Abbreviations: AChR, acetylcholine receptor; LS, least squares; MG-ADL, myasthenia gravis activities of daily living; MuSK, muscle-specific kinase; N, number of subjects in treatment arm; n, number of subjects in specific parameter.

The subgroup analyses of MuSK and AChR autoantibody status to evaluate the efficacy of key secondary endpoint of MG-C in [Table 27](#) and key secondary endpoint of QMG in [Table 28](#) were generated by the FDA statistical reviewer. The results of MuSK and AChR autoantibody statuses including 97.5% CIs on subgroups were from the MMRM using an unstructured covariance matrix. Of note, the sample sizes of the subgroups of MuSK positive and AChR negative were small, thus limiting the ability to produce the multiplicity adjusted 95% CIs with the method used for the primary endpoint and key secondary endpoint.

Change from baseline in MG-C score to day 43 and change from baseline in QMG score to day 43 of rozanolixizumab of ≈7 mg/kg dose level group and rozanolixizumab of ≈10 mg/kg dose level group compared to placebo group in subjects with gMG were generally consistent across subgroups of AChR and MuSK autoantibody status.

Table 27. Summary of Change From Baseline in MG-C Score to Day 43 by Autoantibody Status

Change	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg
MuSK Autoantibody: Positive			
Missing, n/N (%)	1/8 (13)	0/4(0)	1/4 (25)
Change from baseline, LS mean (SE)	-2.57 (2.97)	-9.14 (4.08)	-4.06 (4.23)
Difference from placebo (97.5% CI)	-	-6.57 (-19.49, 6.35)	-1.49 (-14.58, 11.61)
MuSK Autoantibody: Negative			
Missing, n/N (%)	4/59 (7)	1/62 (2)	4/63 (6)
Change from baseline, LS mean (SE)	-1.62 (1.08)	-4.68 (1.08)	-6.66 (1.09)
Difference from placebo (97.5% CI)	-	-3.06 (-5.60, -0.52)	-5.04 (-7.58, -2.51)
AChR Autoantibody: Positive			
Missing, n/N (%)	4/55 (7)	1/60 (2)	4/60 (7)
Change from baseline, LS mean (SE)	-0.27 (2.12)	-3.72 (2.16)	-5.81 (2.16)
Difference from placebo (97.5% CI)	-	-3.46 (-6.07, -0.84)	-5.55 (-8.17, -2.93)

Change	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg
AChR Autoantibody: Negative			
Missing, n/N (%)	1/12 (8)	0/6 (0)	1/7 (14)
Change from baseline, LS mean (SE)	-4.26 (1.96)	-10.93 (2.41)	-7.38 (2.41)
Difference from placebo (97.5% CI)	-	-6.68 (-13.88, 0.52)	-3.13 (-10.06, 3.81)

Source: Reviewer generated analysis based on Applicant submitted data admgcs, adsl.

Abbreviations: AChR, acetylcholine receptor; LS, least squares; MG-C, myasthenia gravis composite; MuSK, muscle-specific kinase

Table 28. Summary of Change From Baseline in QMG Score to Day 43 by Autoantibody Status

Change	Placebo	Rozanolixizumab ≈7 mg/kg	Rozanolixizumab ≈10 mg/kg
MuSK Autoantibody: Positive			
Missing, n/N (%)	1/8 (13)	0/4 (0)	1/4 (25)
Change from baseline, LS mean (SE)	-2.66 (2.71)	-10.28 (3.49)	-5.14 (3.85)
Difference from placebo (97.5% CI)	-	-7.61 (-16.29, 1.06)	-2.48 (-11.46, 6.51)
MuSK Autoantibody: Negative			
Missing, n/N (%)	4/59 (7)	1/62 (2)	4/63 (6)
Change from baseline, LS mean (SE)	-0.78 (0.80)	-4.04 (0.80)	-5.65 (0.81)
Difference from placebo (97.5% CI)	-	-3.27 (-5.16, -1.37)	-4.87 (-6.76, -2.98)
AChR Autoantibody: Positive			
Missing, n/N (%)	4/55 (7)	1/60 (2)	4/60 (7)
Change from baseline, LS mean (SE)	-1.19 (1.57)	-4.66 (1.61)	-6.40 (1.61)
Difference from placebo (97.5% CI)	-	-3.47 (-5.43, -1.51)	-5.21 (-7.18, -3.24)
AChR Autoantibody: Negative			
Missing, n/N (%)	1/12 (8)	0/6 (0)	1/7 (14)
Change from baseline, LS mean (SE)	-2.42 (1.45)	-7.56 (1.57)	-4.19 (1.65)
Difference from placebo (97.5% CI)	-	-5.14 (-9.78, -0.50)	-1.77 (-6.28, 2.74)

Source: Reviewer generated analysis based on Applicant submitted data adqmg, adsl.

Abbreviations: AChR, acetylcholine receptor; LS, least squares; MuSK, muscle-specific kinase; QMG, quantitative myasthenia gravis

Analysis

In Study MG0003, the primary endpoint, change from baseline in MG-ADL score to day 43, and the key secondary endpoints, change from baseline to day 43 in MG-C and QMG scores were evaluated in the overall study population that combined both anti-AChR-gMG and anti-MuSK-gMG subjects. The tables (25, 26, and 27) show comparisons in the primary and the key secondary endpoints between the anti-AChR-gMG and anti-MuSK-gMG subjects. As expected from the disease prevalence, only a small number of subjects with anti-MuSK-gMG (n=16; 8% of the total 200 subjects) were evaluated in the study. Two anti-MuSK-gMG subjects discontinued treatment prematurely one each in the placebo (subject ID: MG0003- (b) (6); day 22) and rozanolixizumab ≈10 mg/kg treatment arms (subject ID: MG0003- (b) (6); received the first two infusions only) due to the lack of efficacy and TEAE of upper abdominal pain and vomiting, respectively. For subject MG0003- (b) (6), the primary endpoint analysis of the MG-ADL change from baseline to the day 85 visit (time interval 43 days) was used according to the prespecified statistical analysis plan (SAP) criterion. The key secondary endpoints QMG and MG-C assessments were not available for the day 85 visit. The subject assigned to placebo did not continue the study during the observation period after treatment discontinuation and therefore had missing data for the primary and key secondary endpoints.

[Table 26](#) shows a difference favoring rozanolixizumab at ≈ 7 mg/kg and ≈ 10 mg/kg doses in the mean change from baseline to day 43 in the MG-ADL total scores (difference from placebo, -6.27 and -4.21 points, respectively).

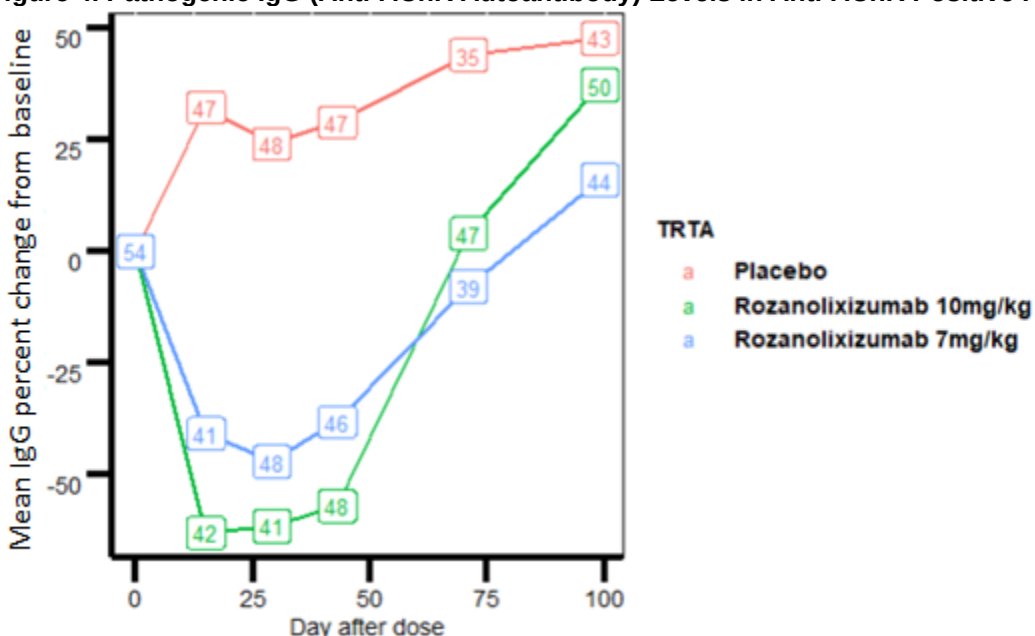
[Table 27](#) and [Table 28](#) show a difference favoring rozanolixizumab in the mean change from baseline to day 43 in the MG-C and QMG scores in the anti-MuSK-MG subjects similar to the anti-AChR-MG subjects over the same period.

None of the subjects receiving rozanolixizumab required rescue therapy. The double-blind treatment period in Study MG0003 consisted of a single treatment cycle. In Study MG0007 OLE study, a consistent improvement from baseline to day 43 in the MG-ADL scores was observed in the subjects with anti-MuSK-gMG during the first 4 treatment cycles (cycle 1, -5.1; cycle 2, -5; cycle 3, -3.8; and cycle 4, -3; $n \leq 8$ per cycle). Similar consistent improvements in the MG-C score and QMG score were observed in the first 4 treatment cycles (Source: MG0007 CSR dated August 17, 2022). However, these MG0007 findings are limited by the absence of placebo-controlled data and the few anti-MuSK-MG subjects.

Pathogenic IgG Levels in Anti AChR-ab and Anti-MuSK-ab Subjects in Study MG0003

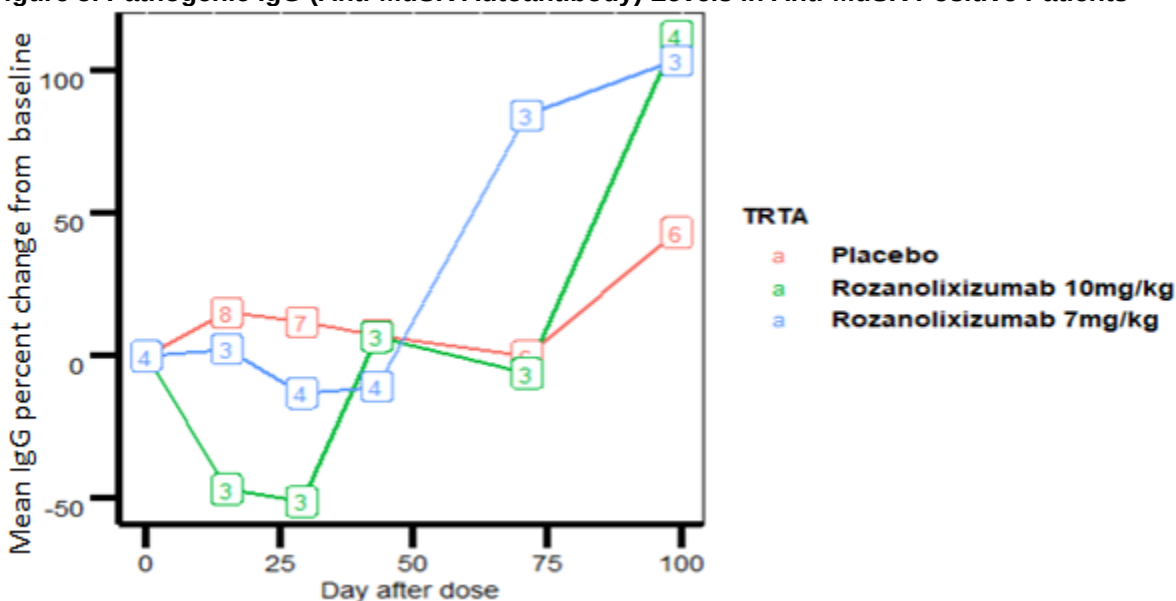
The Applicant collected pathogenic IgG data in Study MG0003. Based on the Applicant's analysis, levels of anti-AChR autoantibodies decreased from baseline for both the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups in a dose-dependent manner. At day 15 (1 week after the second dose), there was a median reduction in anti-AChR autoantibodies of 53.0% for the rozanolixizumab ≈ 7 mg/kg group and 69.9% for the ≈ 10 mg/kg group. The median maximum reduction from baseline in anti-AChR autoantibodies was 73.0% for the rozanolixizumab ≈ 7 mg/kg group and 81.4% for the rozanolixizumab ≈ 10 mg/kg group.

For anti-MuSK autoantibodies, 16 subjects had detectable levels (4, 4, and 8 in subjects in the rozanolixizumab ≈ 7 mg/kg, ≈ 10 mg/kg, and placebo groups, respectively). Per the Applicant, the median maximum reduction from baseline in anti-MuSK autoantibodies was 36.6% for the rozanolixizumab ≈ 7 mg/kg group and 57.8% for the rozanolixizumab ≈ 10 mg/kg group. The review team confirmed these data which can be seen in the plots below (Figure 4, Figure 5). The number inside the box represents the actual number of subjects in that treatment group.

Figure 4. Pathogenic IgG (Anti-AChR Autoantibody) Levels in Anti-AChR Positive Patients

Source: Reviewer generated with data from Study MG0003.

Abbreviations: AChR, acetylcholine receptor; IgG, immunoglobulin G; TRTA, treatment

Figure 5. Pathogenic IgG (Anti-MuSK Autoantibody) Levels in Anti-MuSK Positive Patients

Source: Reviewer generated with data from Study MG0003.

Abbreviations: IgG, immunoglobulin G; MuSK, muscle-specific kinase; TRTA, treatment

Conclusion

These results indicate an improvement in the activities of daily living, motor function, and disease severity in a greater number of subjects treated with rozanolixizumab compared to those treated with the placebo, supporting the clinical efficacy of rozanolixizumab in the anti-AChR-gMG as well as anti-MuSK-gMG subjects. These data are limited by the limited number of anti-

MuSK-gMG subjects. The reviewer notes that the placebo group had more subjects with severe anti-MuSK-gMG (MGFA Class III and IV) compared to those randomized to rozanolixizumab which may have contributed to a more magnified treatment response in the rozanolixizumab treatment groups. However, the mean MG-ADL scores were similar at baseline among the treatment and placebo groups. The data from this study support the Applicant's proposed indication to include anti-AChR-gMG and anti-MuSK-gMG in the product labeling.

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

Issue

Determine the minimum length of time between treatment cycles of rozanolixizumab that is supported by the available efficacy and safety data.

Background

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

“ [REDACTED] (b) (4) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] ”

The Applicant is proposing the dosing regimen of rozanolixizumab as a subcutaneous infusion once weekly for 6 weeks and the subsequent treatment cycles based on clinical evaluation in the draft label. The double-blind, placebo-controlled treatment period in Study MG0003 included 6-weekly infusions, representing one treatment cycle. The dosing regimen in the open-label Study MG0004 consisted weekly infusions up to 52 weeks and the safety data from the first 6 weeks representing a treatment cycle were included in the Safety Pool S1. In the ongoing open-label Study MG0007, subjects are receiving treatment cycles of a subcutaneous infusion once weekly for 6 weeks with repeat treatment cycles administered based on MG symptom worsening. The subjects are assessed every 4 weeks between treatment cycles. The criteria for starting a new treatment cycle are defined as an increase of 2 points on MG-ADL or 3 points on QMG scale between assessments, based on investigator's assessments. It is not usual clinical practice to conduct MG-ADL or QMG scoring during standard clinical care office visits. 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.

As per the protocol study design, the minimum time to start the next treatment cycle is 4 weeks following the last dose of the previous 6-weekly infusions treatment which translates to treatment cycles of 9 weeks. Therefore, the maximum number of completed treatment cycles would be 5 within one year. Refer to Section [7.5](#) for the detailed review of rozanolixizumab exposure and adequacy of the safety database.

Safety Pool S1 consists of all rozanolixizumab-treated subjects who have undergone at least 1 treatment cycle, defined as receiving at least 1 infusion of rozanolixizumab in any 6-week treatment period:

- MG0003 (rozanolixizumab treatment arm only)
- MG0007 (up until the interim cut-off date), and
- MG0004 (the first 6 weeks of data to represent 1 treatment cycle)

Assessment

Exposure to rozanolixizumab in the Randomized, Double-Blind, Placebo-Controlled Study MG0003, Safety Population

In Study MG0003, all subjects received at least 1 rozanolixizumab infusion in 1 treatment cycle. A total of 52 (81.3%) and 48 (69.6%) received all 6 infusions in the treatment cycle in the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups, respectively. The mean number of infusions and mean treatment duration were similar across the treatment groups ([Table 29](#)). Mock infusions using placebo were given to two subjects in each of the rozanolixizumab treatment arms on day 29 and day 36 when IgG levels dropped below 1 g/L to reduce unblinding potential. Note, the data in [Table 29](#) excludes mock transfusions.

Table 29. Exposure to Rozanolixizumab in the Randomized Double-Blind Placebo-Controlled Study MG0003, Safety Population

Exposure	Placebo N=67	RLZ ≈ 7 mg/kg N=64	RLZ ≈ 10 mg/kg N=69
Treatment duration (days)			
Mean (SD)	35.1 (4.1)	35 (5.8)	34.8 (6.4)
Median (min, max)	36 (16, 41)	36 (1, 43)	36 (1, 43)
Subjects treated, by duration, n (%)			
<21 days	1 (1.5)	2 (3.1)	2 (2.9)
≥ 21 to <28 days	3 (4.5)	1 (1.6)	3 (4.3)
≥ 28 to <35 days	5 (7.5)	2 (3.1)	3 (4.3)
≥ 35 to <42 days	58 (86.6)	58 (90.6)	60 (87.0)
≥ 42 days	0	1 (1.6)	1 (1.4)
Number of infusions ¹			
Mean (SD)	5.7 (0.6)	5.7 (0.9)	5.5 (1.0)
Median (min, max)	6.0 (3, 6)	6.0 (1, 6)	6.0 (1, 6)
Number of infusions, n (%) ¹			
1	0	1 (1.6)	1 (1.4)
2	0	1 (1.6)	1 (1.4)
3	1 (1.5)	0	1 (1.4)
4	4 (6.0)	3 (4.7)	7 (10.1)
5	6 (9.0)	7 (10.9)	11 (15.9)
6	56 (83.6)	52 (81.3)	48 (69.6)

Source: adex.xpt and adsl.xpt; Software: R and MG0003 CSR Table 6.2.2

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

¹Excludes mock transfusions

Abbreviations: max, maximum; MG, myasthenia gravis; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration and number of infusions; RLZ, rozanolixizumab

[Table 30](#) shows the duration of MG-ADL response defined as at least two-point improvement or decrease from baseline during the double-blind placebo-controlled treatment cycle in Study MG0003. The proportion of MG-ADL responders was higher in the rozanolixizumab group than placebo group beginning from day 8 (first assessment post-treatment) until day 43 (a week after 6 weekly infusions ended) during the treatment period. The MG-ADL responder rates continued to be higher in the rozanolixizumab treated subjects than placebo group during the majority of visits in the observation period until day 99.

Table 30. MG-ADL Responder Rates by Visit, Randomized Set, Study MG0003

Visit Day	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
	MG-ADL Responder n/Nw (%)	MG-ADL Responder n/Nw (%)	MG-ADL Responder n/Nw (%)
Treatment period			
8	16/67 (23.9)	23/66 (34.8)	25/66 (37.9)
15	14/66 (21.2)	31/62 (50.0)	30/64 (46.9)
22	17/65 (26.2)	38/62 (61.3)	35/64 (54.7)
29	19/64 (29.7)	43/63 (68.3)	35/61 (57.4)
36	22/61 (36.1)	40/63 (63.5)	39/60 (65.0)
43	20/64 (31.3)	46/64 (71.9)	43/62 (69.4)
Observation period			
57	21/54 (38.9)	34/55 (61.8)	39/63 (61.9)
71	19/49 (38.8)	30/52 (57.7)	25/59 (42.4)
85	22/46 (47.8)	26/43 (60.5)	22/47 (46.8)
99	19/64 (29.7)	25/64 (39.1)	27/64 (42.2)

Source: Module 5.3.5.1. MG0003-tables Table 7.3.5

MG-ADL responder is defined as having at least 2-point improvement (decrease) from baseline.

Abbreviations: MG-ADL, myasthenia gravis activities of daily living, N, number of subjects in arm; n, number of subjects meeting criteria; Nw, number of subjects with data

[Table 31](#) shows the MG-ADL score change from baseline to day 43 during the first 4 treatment cycles in Study MG0007. Improvement in the MG-ADL scores were observed from the first post-treatment visit on day 8 through day 43. Similar consistent improvements in the MG-C and QMG scores exceeding the clinically meaningful threshold of 3-points were observed during the first 4 treatment cycles in Study MG0007 (Source: MG0007 CSR dated August 17, 2022).

Table 31. MG-ADL Score Change From Baseline to Day 43 During Each Treatment Cycle, Safety Population, Study MG0007

Treatment Group Statistic	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Change From Baseline	Baseline	Change From Baseline	Baseline	Change From Baseline	Baseline	Change From Baseline	Baseline
RLZ ≈7 mg/kg (N=79)								
n	79	73	54	50	41	35	31	29
Mean (SD)	8.4 (4.2)	-3.6 (3.4)	7.9 (3.6)	-3.0 (3.1)	8 (4)	-3.4 (2.7)	7.6 (3.1)	-4.2 (2.9)
Median (min, max)	8 (0,17)	-3 (-14,4)	7 (1,19)	-3(-12,5)	6(2,20)	-3(-10,1)	7(3,14)	-3(-12,1)
RLZ ≈10 mg/kg (N=78)								
n	76	67	67	63	55	48	39	36
Mean (SD)	8(4)	-3.2(3.2)	9.1(4)	-3.8(3.9)	9(3)	-3.4(3.3)	9.2(3.5)	-3.3(3.2)
Median (min, max)	8(0,18)	-2(-14,2)	8(2,19)	-3(-15,3)	9(3,15)	-3(-11,4)	9(1,16)	-3(-12,1)

Source: MG0007 CSR Table 9-1 dated August 17, 2022

Baseline values were defined as the last available value prior to or on the same date of first administration of study drug at each cycle (i.e., baseline [day 1]) value for that cycle.

Abbreviations: max, maximum; MG-ADL, Myasthenia Gravis Activities of Daily Living; min, minimum; N, number of subjects in treatment arm; n, number of subjects meeting criteria; RLZ, rozanolixizumab

[Table 32](#) shows the time to MG-ADL response defined as at least 2-point improvement or decrease from baseline by treatment cycle during the first 4 treatment cycles in Study MG0007. Median time to MG-ADL response was consistently about 2 weeks for the majority of the treatment cycles. There was a difference in time to MG-ADL response between the rozanolixizumab dose groups in the first cycle (10 days for ≈7 mg/kg vs 23 days for ≈10 mg/kg).

Table 32. Time to MG-ADL Response (≥2.0-Point Improvement From Baseline) During Treatment Cycle, Safety Population, Study MG0007

Treatment Cycle #	Rozanolixizumab ≈7 mg/kg N=79 Median Days (n)	Rozanolixizumab ≈10 mg/kg N=78 Median Days (n)	Rozanolixizumab Total N=157 Median Days (n)
1	10 (79)	23 (78)	15 (157)
2	15 (54)	15 (67)	15 (121)
3	15 (41)	14 (55)	15 (96)
4	9 (31)	14 (39)	12 (70)

Source: MG0007 CSR derived from Table 9-8 on page 154 dated August 17, 2022

Time to MG-ADL response (in days) by study cycle was defined as Date of First MG-ADL Response within study cycle – Date of MG-ADL baseline within study cycle +1.

Subjects who used rescue therapy within cycle or withdrawn from the treatment due to TEAEs before achieving the first MG-ADL response within cycle were censored at the time of the event. Subjects who never achieved a response within cycle were censored at the date of their last MG-ADL assessment.

Abbreviations: MG-ADL, myasthenia gravis activities of daily living, N, number of subjects in arm; n, number of subjects meeting criteria

The Duration of a Treatment Cycle, Safety Pool S1, Studies MG0003, MG0004, and MG0007

As per the 120-day safety update dated March 3, 2023, (eCTD sequence number 0012), there were 88 subjects with at least 5 treatment cycles (the maximum number of cycles possible per year in the study) and a median treatment cycle duration of the fifth cycle was 69.5 days or 9.9 weeks ([Table 33](#)). The average cycle duration was 90.6 days or 12.9 weeks for the cohort of subjects with exactly 5 treatment cycles.

Table 33. Duration of a Treatment Cycle, Safety Pool S1, Studies MG0003, MG0004, and MG0007

Cycle X	Subjects With at Least X Cycles		Cohort of Subjects With a Maximum of X Cycles			
	N (%)	Individual Cycle Duration (Days) ¹	N (%)	Duration of Follow Up (Days) ²		Average Cycle Duration (Days) Based on Median Follow Up ³
		Median (Min/Max)		Mean (SD)	Median ³ (Min/Max)	
1	196 (100)	98 (20, 641)	36 (18.4)	167.2 (171.8)	100 (20, 641)	100
2	160 (81.6)	98 (15, 633)	41 (20.9)	310.4 (171.0)	281 (64, 729)	140.5
3	119 (60.7)	78 (32, 536)	19 (9.7)	471.6 (148.8)	481 (154, 682)	160.3
4	100 (51.0)	77 (31, 324)	12 (6.1)	506 (121.6)	539.5 (298, 667)	134.9
5 ⁴	88 (44.9)	69.5 (4, 204)	21 (10.7)	490.5 (89.4)	453 (361, 690)	90.6
6	67 (34.2)	68 (1, 134)	15 (7.7)	524.7 (110.7)	495 (381, 683)	82.5
7	52 (26.5)	63 (2, 162)	19 (9.7)	508.3 (70.1)	500 (388, 676)	71.4
8	33 (16.8)	61 (3, 112)	13 (6.6)	528.5 (53.8)	534 (437, 619)	66.8
9	20 (10.2)	56 (2, 69)	11 (5.6)	579.4 (57.3)	594 (479, 661)	66.0
10	9 (4.6)	44 (3, 66)	7 (3.6)	613.9 (59.1)	599 (542, 719)	59.9
11	2 (1.0)	41 (38, 44)	2 (1.0)	658.5 (65.8)	658.5 (612, 705)	59.9

Source: Module 2.7.4. 120-day Safety Update Table 1-5

¹The median number of days from the first infusion of a cycle to the first infusion of the next cycle or the data cutoff date, whichever comes first

²The number of days from the first infusion to the end of the observation period (the end of the study or the data cutoff date, whichever comes first)

³The average cycle duration is calculated as the median duration of the follow up divided by the number of the cycles.

⁴the maximum number of cycles possible per one year

Abbreviations: max, maximum; MG, myasthenia gravis; min, minimum; N, number of subjects

For subjects in the Safety Population Pool S1 with more than 12 months' time in Studies MG0003, MG0004, and MG0007, the median duration for the first 5 initiated treatment cycles in one year was 77 days or 11 weeks (n=21 subjects). Twelve subjects completed 5 treatment cycles in one year with the median cycle duration of 70 days or 10 weeks ([Table 34](#)).

Table 34. The Number and Duration of Treatment Cycles per one Year, Safety Pool S1, Studies MG0003, MG0004, and MG0007

Number of Cycles	Subjects with > 12 months' time in studies, Safety Pool S1 Rozanolixizumab total (N = 109)			
	Number of subjects with X initiated cycles per one year ^a n (%)	Average initiated cycle duration ¹ (Days)	Number of subjects with X completed ² cycles per one year ^a n (%)	Average completed cycle duration ¹ (Days)
X = 1	4 (3.7)	NA	18 (16.5)	NA
2	21 (19.3)	100.0	21 (19.3)	98.0
3	19 (17.4)	156.0	30 (27.5)	110.0
4	15 (13.8)	98.0	21 (19.3)	77.0
5	21 (19.3)	77.0	12 (11.0)	70.0
6	24 (22.0)	63.0	4 (3.7)	62.5

N, number of subjects in Safety Pool S1 with > 12 months' time in studies; n, number of subjects with respective number of cycles; NA = Not applicable; X = number of cycles

^aper one year = in the first year

¹ average = median; cycle duration = the time to initiate a repeat treatment cycle from the start of the previous treatment cycle in study; the previous cycle (X-1) was utilized only

²Completed Cycles consists of 6 weekly infusions

Reference: ISS Table 4.6.1.1; [Table 1a](#) and [Table 1b](#)

Source: resp-20230303-clinical-ir-question1.pdf ; eCTD sequence number 0017

For the repeated cyclical treatment Study MG0007, the median cycle duration per one year for the first 5 initiated treatment cycles (n=8 subjects) and completed treatment cycles (n=7 subjects) was 77 days or 11 weeks ([Table 35](#)).

Table 35. The Number and Duration of Treatment Cycles Per One Year, Safety Population, Study MG0007

Number of Cycles	Subjects with > 12 months' time in Study MG0007 Rozanolixizumab total (N = 49)			
	Number of subjects with X initiated cycles per one year ^a n (%)	Average initiated cycle duration ¹ (Days)	Number of subjects with X completed ² cycles per one year ^a n (%)	Average completed cycle duration ¹ (Days)
X = 1	7 (14.3)	NA	6 (12.2)	NA
2	9 (18.4)	156.0	8 (16.3)	148.5
3	4 (8.2)	138.5	9 (18.4)	71.0
4	4 (8.2)	108.5	9 (18.4)	70.0
5	8 (16.3)	77.0	7 (14.3)	77.0
6	14 (28.6)	67.0	3 (6.1)	64.0

N, number of subjects in Study MG0007 with > 12 months' time in study; n, number of subjects with respective number of cycles; NA = Not applicable; X = number of Cycles

^aper one year = in the first year

¹ average = median; cycle duration = the time to initiate a repeat treatment cycle from the start of the previous treatment cycle in study; the previous cycle (X-1) was utilized only

²Completed Cycles consists of 6 weekly infusions

Source: [Table 2a](#), [Table 2b](#) and [Table 2c](#)

Source: resp-20230303-clinical-ir-question1.pdf; eCTD sequence number 0017

The minimum time for a treatment cycle within the first year in the Safety Pool S1 was 63 days or 9 weeks which was protocol-defined based on the combination of the 6-week treatment period and at least 4-week follow-up period. The minimum time for a treatment cycle in Study MG0007 within the first year was 64 days or 9 weeks which is similar to that observed in the combined Safety pool S1 data.

The median treatment-free interval defined as the time from the last dose in the previous treatment cycle to first dose in the subsequent cycle was consistent between the rozanolixizumab dose groups in the Safety Population S1. The median interval was ≈9 weeks between cycles 1 and 2, ≈7 to 8 weeks between cycles 2 and 3, and ≈5 weeks between cycles 3 and 4 and cycles 4 and 5 (MG0007 CSR Section 9.1.9 dated August 17, 2022). Note that the minimum time to initiate a repeat treatment cycle from the last dose in the previous cycle was 4 weeks as defined by the protocol in Study MG0007.

Conclusion

Treatment periods should be 6 weekly SC infusions, as was conducted in the pivotal efficacy Study MG0003. Based on the data from the cyclical OLE treatment Study MG0007, the median time to retreatment for the maximum feasible 5 treatment cycles per year should be 5 weeks from the last dose in the previous treatment cycle to first dose in the subsequent cycle per year.

Safety data are limited on treatment cycles shorter than 9 weeks (6 weekly SC infusions followed by 4 weeks observation period), based on the minimum protocol-defined intertreatment cycle

periods in Study MG0007. However, this should allow most patients' gMG to be treated when it is anticipated to be clinically indicated (i.e., approximately 5 weeks after completion of the previous treatment cycle). The reviewer recommends informing prescribers that the safety of initiating subsequent cycles sooner than 63 days or 9 weeks from the start of the previous treatment cycle has not been established for rozanolixizumab.

6.3.3. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Issue

Determine if the Applicant's proposed 2-fixed dosing regimen of rozanolixizumab for treatment of gMG patients is adequate.

Background

The Applicant has made efforts to simplify the rozanolixizumab dosing regimen throughout the clinical development program. Initially, weight-based dosing was employed in early phase 1 and phase 2 studies. This was followed by the implementation of weight-tiered dosing in the gMG phase 3 studies ([Table 36](#)). The Applicant proposed a 2-fixed dosing regimen for labeling: (b) (4) and 420 mg for patients weighing (b) (4) <50 kg.

Table 36. Generalized Myasthenia Gravis Phase 3 Dose Levels and Weight Tiers and Proposed Fixed Doses

Body weight	Rozanolixizumab doses in Phase 3 program		Proposed fixed doses	Primary evidence to support dose
	≈7mg/kg	≈10mg/kg		
(b) (4) <50kg	280mg	420mg	420mg	MG0003 and MG0007 clinical E&S
≥50 to <70kg	(b) (4)		(b) (4)	MG0003 and MG0007 clinical E&S
≥70 to <100kg				MG0003 and MG0007 clinical E&S
≥100kg				Modeling and simulation

≈=approximate dose; E&S=efficacy and safety

Source: The Applicant's Clinical Overview Page 25, Table 3-1

Table 37. Applicant's Proposed Dose Based on Body Weight

Body weight of patient	Dose
(b) (4) <50 kg	420 mg
(b) (4)	(b) (4) mg

Source: The Applicant's draft label, Page 2, Table 1

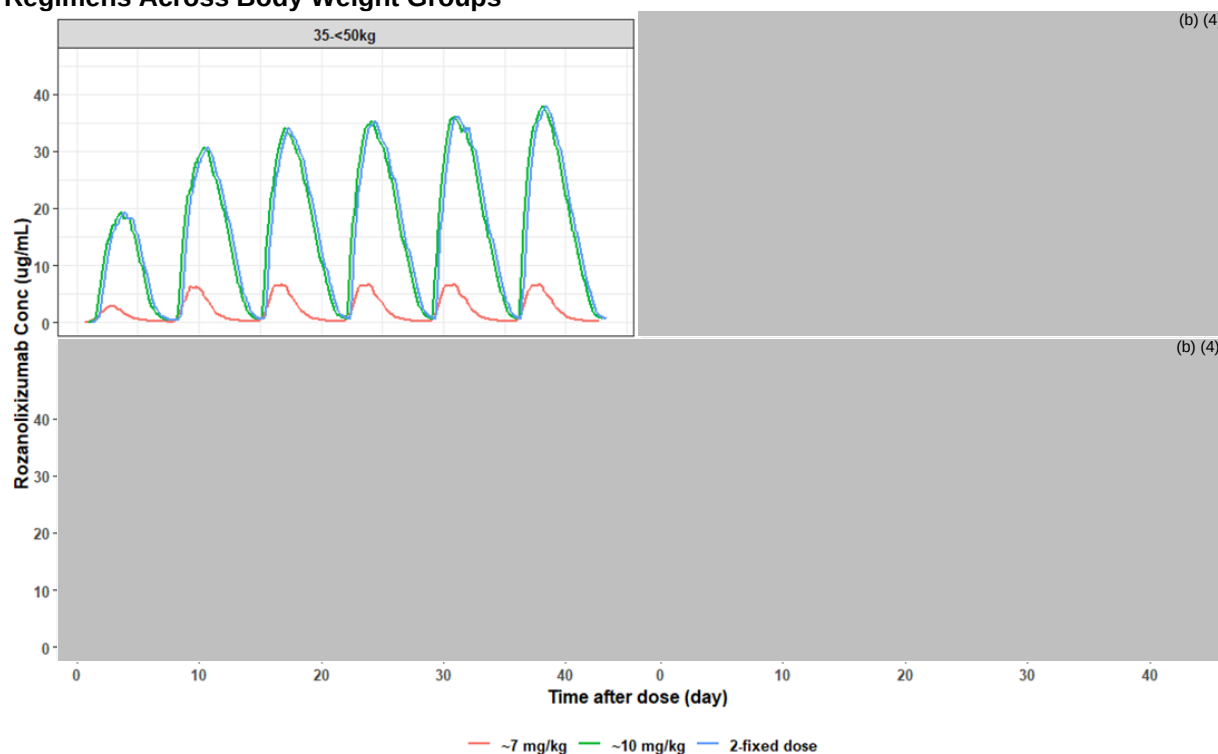
Assessment

The Applicant's 2-fixed dose regimen in patients weighing less than 100 kg is consistent (either ≈ 7 mg/kg or ≈ 10 mg/kg) with the weight-tiered regimen in subjects less than 100 kg evaluated in MG0003 and is acceptable from a clinical pharmacology perspective.

However, in subjects weighing 100 kg or more, the proposed dose of (b) (4) mg is (b) (4) the weight-tiered regimen (≈ 7 mg/kg or ≈ 10 mg/kg) evaluated in Study MG0003. Additional exploratory analyses suggest that in subjects weighing 100 kg or more, drug exposures may be lower than those following either of the doses (≈ 7 mg/kg or ≈ 10 mg/kg) evaluated in MG0003 (Figure 6, below. Refer to Section 14.5. for more details). It is unclear if these dose/exposure differences translate into clinically relevant differences in total IgG, anti-AChR or anti-MuSK IgG and/or clinical endpoint (MG-ADL).

Based on these considerations, the clinical pharmacology review team recommends 840 mg in patients weighing 100 kg or more, as evaluated in MG0003. The Applicant was informed of the review team's recommendation, and concurred.

Figure 6. PK Simulation of Six Weekly SC Infusion of Rozanolixizumab for Different Dose Regimens Across Body Weight Groups



Source: Reviewer's Analysis.

Note: Doses for the 2-fixed dose regimen are 420 mg in patients weighing <50 kg and (b) (4) Q1W). For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈ 7 mg/kg: 35 to <50 kg: 280 mg, 50 to <70 kg: 420 mg, 70 to <100 kg: 560 mg, ≥ 100 kg: 840 mg; for ≈ 10 mg/kg: 35 to <50 kg: 420 mg, 50 to <70 kg: 560 mg, 70 to <100 kg: 840 mg, ≥ 100 kg: 1120 mg).

Note: Six weekly doses were simulated for each dosing regimen.

Abbreviations: $\approx/\approx$, approximate dose; Q1W, once a week; SC, subcutaneous

Conclusion

In summary, considering that subjects weighing 100 kg or more comprise 23% of the phase 3 study population, there is a concern regarding underdosing in patients weigh 100 kg or more. For subjects weighing 100 kg or more, the efficacy of rozanolixizumab at proposed fixed dose regimen of (b) (4) mg cannot be reliably predicted. Therefore, we recommend 840 mg for subjects weighing 100 kg or more, as evaluated in Study MG0003. This recommendation leads to a modification in the dose table, as illustrated below.

Table 38. Recommended Dose by Body Weight (Modified by FDA Reviewer)

Body Weight of Patient	Dose
<50 kg	420 mg
≥50 kg to <100 kg	560 mg
≥100 kg	840 mg

Source: FDA clinical pharmacology reviewer

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No adverse effects were seen in male and female cynomolgus monkeys administered subcutaneous (SC) doses of up to 150 mg/kg UCB7665 every 3 days for 4, 13, and 26 weeks.

In an enhanced pre- and postnatal development (ePPND) study, 3 groups of 19 pregnant female cynomolgus monkeys were administered SC injections of 0, 50, and 150 mg/kg UCB7665 SC every 3 days over the period of organogenesis (i.e., gestational day 20 until birth). Adverse effects consisted of early embryonic loss, reduced infant body weight, and impaired immune function in infants. There was no NOAEL for adverse effects in the ePPND study.

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

Rozanolixizumab is a humanized anti-FcRn immunoglobulin G subclass 4 monoclonal antibody (IgG4p) monoclonal antibody that is proposed to block FcRn leading to enhanced IgG catabolism.

Hypoalbuminemia was of concern because the Fc receptor is involved in the maintenance of serum albumin levels. Hypoalbuminemia is discussed in Section [7.7.5](#).

Infections were of special interest because Fc receptor inhibition results in a reduction of circulating IgG, which potentially increases the risk of infection. Infections are discussed in Section [7.7.1](#).

Cholesterol levels were of concern because elevated low-density lipoprotein (LDL) cholesterol levels led to premature termination of a phase 2 study (NCT03938545) after 12 weeks of treatment with RVT-1401, a human monoclonal antibody targeting FcRn developed for the treatment of subjects with Graves' ophthalmopathy ([Men et al. 2021](#)). However, a safety signal for elevated lipids was not identified in subjects treated with efgartigimod. Cholesterol levels are discussed in Section [7.6.2.6](#).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

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

7.3.1. Adverse Events Identified in Postmarket Experiences

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

7.3.2. Expectations on Safety

There was an increased frequency of infections, including serious infections and serious adverse events of aseptic meningitis in subjects treated with rozanolixizumab during clinical trials.

Uncertainty exists in whether safety outcomes of infections would be potentially more serious in an unmonitored postmarket setting particularly in individuals with a greater risk of immunosuppression, such as the intended patient population with gMG.

Hypersensitivity reactions including angioedema and rash have occurred in subjects treated with rozanolixizumab in clinical trials. Uncertainty exists in whether these safety outcomes would be potentially more serious in a more unmonitored outpatient setting.

The safety and effectiveness of rozanolixizumab have not been established in patients with purely ocular MG, severe gMG, those with impending MG crisis or with MG crisis, and those who do not have detectable anti-AChR or anti-MuSK antibodies (seronegative MG) in clinical trials.

The safety and effectiveness of rozanolixizumab in women who are pregnant, or breast-feeding have not been characterized in clinical trials. Because rozanolixizumab will be used in women of childbearing potential, a pregnancy outcome study is recommended as a postmarketing requirement (see Section [23](#)).

The risk of reactivation of tuberculosis and hepatitis has not been characterized. The risk of malignancy is not known.

Immunization with vaccines during rozanolixizumab treatment has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with any vaccine are unknown.

Concomitant use of other medications that bind to the human FcRn may reduce the effectiveness of these compounds and that of rozanolixizumab.

7.3.3. Additional Safety Issues From Other Disciplines

Vyvgart (efgartigimod alfa), also an FcRn blocking monoclonal antibody, was approved for the treatment of myasthenia gravis on December 17, 2021. Although IgG levels were reduced, a signal for infections were not seen in nonclinical studies. Data from clinical studies led to listing infection under Warnings and Precautions in the Vyvgart® label. The section stipulates monitoring for infections and, if serious infections occur, to consider withholding administration until the infection is resolved.

7.4. FDA Approach to the Safety Review

Clinical study data were provided by the clinical data scientist support team and independently analyzed using JMP software. 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 adverse events (AEs). The Applicant's translations of verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in Studies MG0003, MG0004, and MG0007 were found to be acceptable. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0 was used as a supportive tool to evaluate AEs; however, the final intensity of AEs was graded as mild, moderate, or severe by the investigator based on clinical judgement.

Data from the pivotal double-blind, placebo-controlled Study MG0003 and the open-label extension Studies MG0004 and MG0007 formed the basis of the clinical safety evaluation ([Table 39](#)). Study MG0003 is the primary source of evidence of effectiveness, and the results of this study are presented individually in this review. The MG0003 study data include findings that occurred in subjects who received one (1) double-blind, placebo-controlled, six-week treatment cycle, which is the maximum number a subject could receive by protocol. Safety data from Study MG0003 will provide the primary description of safety, with Studies MG0004 and MG0007 providing supportive data.

Table 39. Clinical Studies Contributing to the Integrated Review of Safety

Study	Dose	Subjects in Double-Blind Safety Set	Subjects in Open-Label Safety Set
MG0003	RLZ ≈7 mg/kg or RLZ ≈10 mg/kg or Placebo	RLZ ≈7 mg/kg (n=64) RLZ ≈10 mg/kg (n=69) Placebo (n=67)	N/A
MG0004 ^a	RLZ ≈7 mg/kg or RLZ ≈10 mg/kg	N/A	RLZ ≈7 mg/kg (n=50) RLZ ≈10 mg/kg (n=42)
MG0007 ^a	RLZ ≈7 mg/kg or RLZ ≈10 mg/kg	N/A	RLZ ≈7 mg/kg (n=98) RLZ ≈10 mg/kg (n=96)
Safety pool S1 ^b	RLZ ≈7 mg/kg or RLZ ≈10 mg/kg		Total RLZ (n=196) ^c RLZ ≈7 mg/kg (n=95) RLZ ≈10 mg/kg (n=101)

Source: Module 2.7.4. Summary of Clinical Safety September 29, 2022

^a Subjects who switched doses may be counted in both RLZ doses.

^b (MG0003 RLZ data only, MG0007, MG0004 first 6 weeks only).

^c Same number of subjects included in the 120-day safety update dated February 3, 2023, eCTD Sequence number 0012

Abbreviations: MG, myasthenia gravis; N/A, not applicable; RLZ, rozanolixizumab; ≈, approximately dose per bodyweight

In Study MG0003, the treatment-emergent adverse events (TEAEs) were protocol-defined as any adverse event regardless of relatedness to the study drug occurring during the 6-week treatment period followed by an 8-week (56 days) observation period.

Pool S1 consisted of all rozanolixizumab-treated subjects who have undergone at least one (1) treatment cycle, defined as receiving at least 1 infusion of rozanolixizumab in any 6-week treatment period. This pool includes data from MG0003 and MG0007 (until data cut-off July 8, 2022, 120-day safety update data cutoff date October 7, 2022) and the first 6 weeks of data from MG0004. For Safety Pool S1, the treatment-emergent adverse events were protocol-defined as,

- Study MG0003: Adverse event starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose in the treatment cycle.
- Study MG0004 (first 6 weeks of all study subjects): Adverse event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the treatment period or 8 weeks after the last rozanolixizumab administration in subjects who discontinued the study or rozanolixizumab
- Study MG0007: Adverse event starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle

Any AEs occurring ≥8 weeks after the last infusion and before the next treatment cycle (intermittent period) were defined as non-TEAEs in Studies MG0003 and MG0007.

Section 7.6.2 presents the safety data for the pivotal double-blind, placebo-controlled Study MG0003 alone. Section 17 presents pooled data Safety Pool S1 for Study MG0003, the first 6-week of treatment in Study MG0004, and the ongoing open-label cyclical treatment extension Study MG0007.

Refer to Section 6.2.2 and Section 15 for the detailed description of the study design, eligibility criteria, objectives, and endpoints, and permitted standard of care treatment in Study MG0003 and the open-label extension Studies MG0004 and MG0007, respectively.

7.5. Adequacy of the Clinical Safety Database

IND132407 Information Request Advice dated February 10, 2022, stated:

“Typically, we would require a biologics license application (BLA) submission for a rare disease, such as generalized myasthenia gravis, to be consistent with the International Conference for Harmonization (ICH E1) requirements that 100 subjects be exposed to the drug for a minimum of one year, with at least half of the safety database consisting of patients dosed with the highest anticipated dose and frequency. There may be some flexibility with these requirements.”

IND132407 preBLA Meeting Preliminary Comments dated July 19, 2022, stated:

“Your proposed safety database appears capable of supporting a BLA submission for the treatment of gMG. The adequacy of the drug exposure in terms of the number of infusions in a treatment cycle, the duration of a treatment cycle, the number of treatment cycles per year, and the time to initiate a repeat treatment cycle from the start of the previous treatment cycle will be a matter of review. Your submission should include information on the duration of treatment cycles in Pool S1.”

As per the preBLA request the Applicant provided the rozanolixizumab exposure data from subjects in Safety Pool S1 including the data from the 120-day safety update (eCTD seq 0012) which is reviewed below:

The Number of Infusions in a Treatment Cycle, Safety Pool S1, Studies MG0003, MG0004, and MG0007

In Safety Pool S1, 196 subjects received a total of 4,557 infusions (mean: 23.3; SD: 15.7; median: 19.5, range: 1, 65), representing a mean of 5.4 infusions per treatment cycle (source: Module 2.7.4; 120-Day SU Table 4.2.1 eCTD seq 0012). A total of 578 treatment cycles of 6 infusions were administered in 196 subjects and the median number of completed cycles was 2 with the range of 0 to 10 cycles. The total number of cycles including incomplete initiated cycles (at least 1 infusion but less than 6 infusions) was 846 with the median 4 and range 1 to 11. Of 846 cycles, 86 cycles in 86 subjects were fixed and 760 cycles were symptom-driven in 196 subjects.

The Number and Duration of Treatment Cycle During the Entire Study Period, Safety Pool S1, Studies MG0003, MG0004, and MG0007

As per the 120-day safety update, 196 (100%) subjects in the Safety Pool S1 received at least one infusion of rozanolixizumab (Table 40). The number of subjects with more than 12 months' time in the studies was 133, and of these subjects, 100 (75.2%) subjects had at least four treatment cycles with the median fourth treatment cycle duration of 77 days (11 weeks). There were 88 (66.1%) subjects with at least 5 treatment cycles (the maximum number of treatment cycles

possible per year according to the protocol) completed during the entire study duration and the median fifth treatment cycle duration was 69.5 days or 9.9 weeks. The average cycle duration was 90.6 days or 12.9 weeks for the cohort of 21 subjects with exactly five treatment cycles.

The median treatment-free interval defined as the time from last dose in the previous treatment cycle to first dose in the subsequent cycle was consistent between the rozanolixizumab dose groups in the Safety Population Pool S1. The median interval was $\approx$ 9 weeks between cycles 1 and 2, $\approx$ 7 to 8 weeks between cycles 2 and 3, and $\approx$ 5 weeks between cycles 3 and 4 and cycles 4 and 5 (MG0007 CSR Section 9.1.9 dated August 17, 2022).

Table 40. Duration of a Treatment Cycle, Safety Pool S1, Studies MG0003, MG0004, and MG0007

Cycle X	Subjects With at Least X Cycles		Cohort of Subjects With a Maximum of X Cycles			
	N (%)	Individual Cycle Duration (Days) ¹	N (%)	Duration of Follow Up (Days) ²	Median ³ (Min/Max)	Average Cycle Duration (Days) Based on Median Follow Up ³
		Median (Min/Max)		Mean (SD)		
1	196 (100)	98 (20, 641)	36 (18.4)	167.2 (171.8)	100 (20, 641)	100
2	160 (81.6)	98 (15, 633)	41 (20.9)	310.4 (171.0)	281 (64, 729)	140.5
3	119 (60.7)	78 (32, 536)	19 (9.7)	471.6 (148.8)	481 (154, 682)	160.3
4	100 (51.0)	77 (31, 324)	12 (6.1)	506 (121.6)	539.5 (298, 667)	134.9
5 ⁴	88 (44.9)	69.5 (4, 204)	21 (10.7)	490.5 (89.4)	453 (361, 690)	90.6
6	67 (34.2)	68 (1, 134)	15 (7.7)	524.7 (110.7)	495 (381, 683)	82.5
7	52 (26.5)	63 (2, 162)	19 (9.7)	508.3 (70.1)	500 (388, 676)	71.4
8	33 (16.8)	61 (3, 112)	13 (6.6)	528.5 (53.8)	534 (437, 619)	66.8
9	20 (10.2)	56 (2, 69)	11 (5.6)	579.4 (57.3)	594 (479, 661)	66.0
10	9 (4.6)	44 (3, 66)	7 (3.6)	613.9 (59.1)	599 (542, 719)	59.9
11	2 (1.0)	41 (38, 44)	2 (1.0)	658.5 (65.8)	658.5 (612, 705)	59.9

Source: Module 2.7.4. 120-Day Safety Update Table 1-5

¹The median number of days from the first infusion of a cycle to the first infusion of the next cycle or the data cutoff date, whichever comes first

²The number of days from the first infusion to the end of the observation period (the end of the study or the data cutoff date, whichever comes first)

³The average cycle duration is calculated as the median duration of the follow up divided by the number of the cycles.

⁴the maximum number of cycles possible per one year

Abbreviations: max, maximum; MG, myasthenia gravis; min, minimum; N, number of subjects

The Number and Duration of Treatment Cycle During the First Year in the Studies, Safety Pool S1, Studies MG0003, MG0004, and MG0007

As per the response to the information request dated March 3, 2023, eCTD seq 0017, out of 109 subjects with more than 12 months' time in Studies MG0003, MG0004, and MG0007 at the time of the original BLA, 21 (19.3%) subjects had initiated 5 treatment cycles in the first year and 12 (11%) subjects had completed 5 treatment cycles in the same year ([Table 41](#)). The median cycle duration for the five initiated cycles was 77 days (11 weeks) and for five completed cycles was 70 days (10 weeks). There were 24 subjects who had initiated six treatment cycles in the first year (the maximum possible initiated treatment cycles per year according to study protocol) with the median cycle duration of 63 days or nine weeks.

The minimum time for a treatment cycle within the first year in the Safety Pool S1 was 63 days or 9 weeks which was consistent with that defined in the protocol based on the combination of the 6-weekly infusion treatment period (5 weeks) and at least 4-week follow-up period.

Table 41. The Number and Duration of Treatment Cycles During the First Year, Safety Pool S1, Studies MG0003, MG0004, and MG0007

Number of Cycles	Subjects with > 12 months' time in studies, Safety Pool S1 Rozanolixizumab total (N = 109)			
	Number of subjects with X initiated cycles per one year ^a n (%)	Average initiated cycle duration ¹ (Days)	Number of subjects with X completed ² cycles per one year ^a n (%)	Average completed cycle duration ¹ (Days)
X = 1	4 (3.7)	NA	18 (16.5)	NA
2	21 (19.3)	100.0	21 (19.3)	98.0
3	19 (17.4)	156.0	30 (27.5)	110.0
4	15 (13.8)	98.0	21 (19.3)	77.0
5	21 (19.3)	77.0	12 (11.0)	70.0
6	24 (22.0)	63.0	4 (3.7)	62.5

N, number of subjects in Safety Pool S1 with > 12 months' time in studies; n, number of subjects with respective number of cycles; NA = Not applicable; X = number of cycles

^aper one year = in the first year

¹ average = median; cycle duration = the time to initiate a repeat treatment cycle from the start of the previous treatment cycle in study; the previous cycle (X-1) was utilized only

²Completed Cycles consists of 6 weekly infusions

Reference: ISS Table 4.6.1.1; [Table 1a](#) and [Table 1b](#)

Source: resp-20230303-clinical-ir-question1.pdf; eCTD sequence number 0017

The Number and Duration of Treatment Cycle During the First Year in the Study, Safety Population, Study MG0007

For both the 109 and 133 subjects with more than 12 months participation at the original BLA and 120-day safety update data cuts respectively, within the first year the median number of cycles initiated was four per year (range: 1 to 7) (Source: 120-day safety update dated February 3, 2023, eCTD Sequence number 0012).

As per the response to the information request dated March 3, 2023, out of 49 subjects with more than 12 months' time in the open-label repeated cyclical treatment Study MG0007, eight subjects had initiated five treatment cycles and seven subjects had completed five treatment cycles in the first year. For both subcohorts, the median cycle duration in the first year was 77 days or 11 weeks ([Table 42](#)). The median treatment cycle duration was 67 days or 9.6 weeks in the same year in 14 subjects who had initiated the maximum possible six treatment cycles.

The minimum time for a treatment cycle in Study MG0007 within the first year was 64 days or 9 weeks which is similar to that observed in the combined Safety pool S1 data.

Table 42. The Number and Duration of Treatment Cycles the First Year, Safety Population, Study MG0007

Number of Cycles	Subjects with > 12 months' time in Study MG0007 Rozanolixizumab total (N = 49)			
	Number of subjects with X initiated cycles per one year ^a n (%)	Average initiated cycle duration ¹ (Days)	Number of subjects with X completed ² cycles per one year ^a n (%)	Average completed cycle duration ¹ (Days)
X = 1	7 (14.3)	NA	6 (12.2)	NA
2	9 (18.4)	156.0	8 (16.3)	148.5
3	4 (8.2)	138.5	9 (18.4)	71.0
4	4 (8.2)	108.5	9 (18.4)	70.0
5	8 (16.3)	77.0	7 (14.3)	77.0
6	14 (28.6)	67.0	3 (6.1)	64.0

N, number of subjects in Study MG0007 with > 12 months' time in study; n, number of subjects with respective number of cycles; NA = Not applicable; X = number of Cycles

^aper one year = in the first year

¹ average = median; cycle duration = the time to initiate a repeat treatment cycle from the start of the previous treatment cycle in study; the previous cycle (X-1) was utilized only

²Completed Cycles consists of 6 weekly infusions

Source: Table 2a, Table 2b and Table 2c

Source: resp-20230303-clinical-ir-question1.pdf; eCTD sequence number 0017

The reviewer notes that the safety data are limited on treatment cycles shorter than 63 days or 9 weeks, based on the minimum protocol-defined intertreatment cycle periods in the open-label extension Study MG0007. However, this should allow most patients' gMG to be treated when it is anticipated to be clinically indicated (i.e., approximately 5 weeks after completion of the previous treatment cycle). The reviewer recommends informing prescribers that the safety of initiating subsequent cycles sooner than 63 days or 9 weeks from the start of the previous treatment cycle has not been established for rozanolixizumab.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Studies A and B

Not applicable.

7.6.2. Safety Results, Study MG0003

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study MG0003

[Table 43](#) provides a summary of treatment-emergent adverse events (TEAEs) in Study MG0003. The overall frequency of TEAEs was similar between the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups. Relatively more subjects on rozanolixizumab than placebo reported TEAEs. The frequency of severe adverse events and TEAEs leading to drug discontinuation or dose modification was higher in the rozanolixizumab ≈ 10 mg/kg group than rozanolixizumab ≈ 7 mg/kg and placebo groups. There were no deaths.

Table 43. Overview of Treatment-Emergent Adverse Events,¹ Safety Population, Study MG0003²

Event Category	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ³	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ³	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ³
SAE	6 (9.0)	5 (7.8)	-1.1 (-10.6, 8.3)	7 (10.1)	1.2 (-8.7, 11.1)	12 (9.0)	0.1 (-8.3, 8.5)
SAEs with fatal outcome	0	0	0 (0, 0)	0	0 (0, 0)	0	0 (0, 0)
Life-threatening SAEs	0	0	0 (0, 0)	2 (2.9)	2.9 (-1.1, 6.9)	2 (1.5)	1.5 (-0.6, 3.6)
AE leading to permanent discontinuation of study drug	2 (3.0)	2 (3.1)	0.1 (-5.8, 6.0)	5 (7.2)	4.3 (-3.1, 11.6)	7 (5.3)	2.3 (-3.3, 7.8)
AE leading to dose modification of study drug	1 (1.5)	3 (4.7)	3.2 (-2.7, 9.1)	6 (8.7)	7.2 (-0.1, 14.5)	9 (6.8)	5.3 (0.1, 10.4) *
AE leading to interruption of study drug	1 (1.5)	3 (4.7)	3.2 (-2.7, 9.1)	6 (8.7)	7.2 (-0.1, 14.5)	9 (6.8)	5.3 (0.1, 10.4) *
AE leading to reduction of study drug	0	0	0 (0, 0)	0	0 (0, 0)	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0 (0, 0)	0	0 (0, 0)
Other	0	0	0 (0, 0)	0	0 (0, 0)	0	0 (0, 0)
Any AE ⁴	45 (67.2)	52 (81.2)	14.1 (-0.7, 28.8)	57 (82.6)	15.4 (1.1, 29.8) *	109 (82.0)	14.8 (1.8, 27.8) *
Severe and worse	3 (4.5)	3 (4.7)	0.2 (-7.0, 7.4)	13 (18.8)	14.4 (3.9, 24.8) *	16 (12.0)	7.6 (0.1, 15.0) *
Moderate	15 (22.4)	25 (39.1)	16.7 (1.1, 32.2) *	29 (42.0)	19.6 (4.3, 35.0) *	54 (40.6)	18.2 (5.2, 31.2) *
Mild	24 (35.8)	24 (37.5)	-2.8 (-19.5, 13.9)	15 (21.7)	-14.1 (-29.1, 1.0)	39 (29.3)	-11.0 (-25.0, 3.1)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

²Duration is 6 weeks of treatment, followed by 8-week observation period to total 14 weeks.

³Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.

⁴Severity as assessed by the investigator.*potential imbalance between rozanolixizumab and placebo groups

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; RLZ, rozanolixizumab; SAE, serious adverse event

7.6.2.2. Deaths, Study MG0003

There were no deaths in Study MG0003.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study MG0003

The frequency of serious adverse events (SAEs) was balanced between the rozanolixizumab and placebo treatment groups. All SAEs are listed in [Table 44](#) and [Table 45](#).

Worsening of Myasthenia Gravis

[Table 46](#) summarizes seven subjects who had worsening of MG and required the use of rescue therapy or missed treatment in Study MG0003. Two subjects on placebo developed MG crisis, whereas none of the subjects developed MG crisis while receiving rozanolixizumab treatment in Study MG0003. Five subjects had worsening of MG symptoms including one in the placebo group and two each in the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups. Two subjects were withdrawn from the placebo group due to MG worsening and crisis. Three subjects in the rozanolixizumab treatment groups required IVIg due to MG worsening during observation period in Study MG0003; none had interruptions in study treatment. One subject in the rozanolixizumab ≈ 7 mg/kg treatment group had MG worsening due to severe vomiting and aspiration pneumonia and recovered without rescue therapy; this subject missed the second infusion and received a total of five doses in Study MG0003.

Infections

No serious infections were reported in the subjects receiving rozanolixizumab in Study MG0003. There was a single event of serious COVID-19 pneumonia in one subject MG0003/ (b) (6) in the placebo arm and symptoms resolved in 8 days; the subject missed fourth and sixth placebo infusions during randomized treatment period in Study MG0003.

Headache

Subject ID MG0003/ (b) (6) experienced a serious headache 10 days after the first and third day after the most recent rozanolixizumab ≈ 10 mg/kg infusion. This subject was admitted overnight to a hospital due to logistical reasons. The subject woke up with moderately severe throbbing and pressurized headache. There was exacerbation with light, sound, and movement. The subject had nausea but no vomiting, fever, or neck stiffness. Headache and nausea resolved in 2 days with ibuprofen and metoclopramide. There were no study drug dose modification or interruption. The subject had no previous history of headaches or migraine. The SAE of severe headache was likely related to rozanolixizumab due to the suggestive time to onset and a history of positive rechallenge (not as severe headache as the first episode).

Seizure

Subject ID MG0003/ (b) (6) was a 71-year-old subject randomized to rozanolixizumab ≈ 7 mg/kg treatment group developed two episodes of seizures during observation period in

Study MG0003. Hospital notes indicated tonic seizures; no other clinical description provided in narrative. The CT head was normal. Etiology of the seizure is unclear. The event was considered resolved and the relation of causality to rozanolixizumab cannot be ruled out.

Acute Respiratory Failure

Subject ID MG0003/ (b) (6) was randomized to rozanolixizumab ≈ 10 mg/kg treatment in Study MG0003. The subject was on concomitant medications for standard MG care including prednisone, mycophenolate, and pyridostigmine. The subject developed severe acute respiratory failure in the setting of tracheostomy device dislocation, tracheal stenosis, and lobar pneumonia (severe acute respiratory syndrome coronavirus 2 negative). This subject required tracheostomy for tracheal device dislocation, did not require ventilatory assistance, treated with antibiotics, the SAE occurred 43 days after the first and seventh day after the last infusion and resolved in 28 days from the onset. The subject discontinued the study due to the device dislocation. Note that this subject developed pyrexia 4 days after the first infusion and later again 29 days after the first infusion, which responded to paracetamol and resolved in 24 hours. The SAE of acute respiratory failure was unlikely related to rozanolixizumab because the subject experienced the SAE due to the tracheal device dislocation. The reviewer notes that the subject was diagnosed with pneumonia which responded to antibiotics during hospitalization and considered resolved; the event of pneumonia was not reported as SAE, and the relation of causality to rozanolixizumab for pneumonia cannot be ruled out.

Other SAEs in the Subjects on Rozanolixizumab Treatment

Other SAEs included gastritis, vomiting, chest pain, joint pain, nephrolithiasis, cervical dysplasia, metastatic squamous cell carcinoma, and tracheal device dislocation.

Table 44. Subjects With Serious Treatment-Emergent Adverse Events¹ by System Organ Class and Preferred Term, Safety Population, Study MG0003²

System Organ Class Preferred Term ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ⁴
Any SAE	6 (9.0)	5 (7.8)	-1.1 (-10.6, 8.3)	7 (10.1)	1.2 (-8.7, 11.1)	12 (9.0)	0.1 (-8.3, 8.5)
Gastrointestinal disorders (SOC)	0	2 (3.1)	3.1 (-1.1, 7.4)	0	0 (0, 0)	2 (1.5)	1.5 (-0.6, 3.6)
Gastritis	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Vomiting	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
General disorders and administration site conditions (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Chest pain	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Infections and infestations (SOC)	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
COVID-19 pneumonia	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Injury, poisoning and procedural complications (SOC)	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Thoracic vertebral fracture	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Musculoskeletal and connective tissue disorders (SOC)	1 (1.5)	1 (1.6)	0.1 (-4.1, 4.3)	0	-1.5 (-4.4, 1.4)	1 (0.8)	-0.7 (-4.0, 2.5)
Arthralgia	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Muscular weakness	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Metastatic squamous cell carcinoma	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Nervous system disorders (SOC)	3 (4.5)	2 (3.1)	-1.4 (-7.9, 5.2)	3 (4.3)	-0.1 (-7.0, 6.8)	5 (3.8)	-0.7 (-6.6, 5.2)
Seizure	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Myasthenia gravis	1 (1.5)	1 (1.6)	0.1 (-4.1, 4.3)	2 (2.9)	1.4 (-3.5, 6.3)	3 (2.3)	0.8 (-3.1, 4.6)
Headache	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Myasthenia gravis crisis	2 (3.0)	0	-3.0 (-7.1, 1.1)	0	-3.0 (-7.1, 1.1)	0	-3.0 (-7.1, 1.1)
Product issues (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Device dislocation	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)

System Organ Class Preferred Term ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ⁴
Renal and urinary disorders (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Nephrolithiasis	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Reproductive system and breast disorders (SOC)	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Cervical dysplasia	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Acute respiratory failure ⁵	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.³Coded as MedDRA preferred terms.⁴Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.⁵unrelated to myasthenia gravis and study intervention

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; RLZ, rozanolixizumab.; SOC, system organ class

Table 45. Subjects With Serious Treatment-Emergent Adverse Events¹ by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study MG0003²

System Organ Class (SOC) FMQ (Narrow) ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ⁴
Gastrointestinal disorders (SOC)							
Vomiting	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Infections and infestations (SOC)							
Viral Infection	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Musculoskeletal and connective tissue disorders (SOC)							
Arthralgia	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Fracture	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Osteoporosis	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)

System Organ Class (SOC) FMQ (Narrow) ³	Placebo	RLZ≈7 mg/kg	RLZ≈7 mg/kg vs. Placebo	RLZ≈10 mg/kg	RLZ≈10 mg/kg vs. Placebo	RLZ Total	RLZ Total vs. Placebo
	N=67 n (%)	N=64 n (%)	Risk Difference (%) (95% CI) ⁴	N=69 n (%)	Risk Difference (%) (95% CI) ⁴	N=133 n (%)	Risk Difference (%) (95% CI) ⁴
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)							
Malignancy	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Nervous system disorders (SOC)							
Seizure	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Headache	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Respiratory, thoracic and mediastinal disorders (SOC)							
Respiratory Failure ⁵	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

³Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

⁴Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.

⁵unrelated to myasthenia gravis and study intervention.

Abbreviations: FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab; SOC, system organ class

Table 46. Worsening of Myasthenia Gravis: Use of Rescue Therapy and Missing Treatment, Study MG0003

Subject ID	Study Arm	MedDRA PT	Time Between Onset and First Infusion (Days)	Time Between Onset and Last Infusion (Days)	Duration (Days)	Intensity (Relation to Study Drug)	Outcome
MG0003 / (b) (6)	Placebo	MG crisis	36	1 (6 th and final infusion)	6	Moderate SAE (unrelated)	Resolved with IVIg unchanged AZT, prednisone, pyridostigmine completed the Study MG0003 and enrolled in MG0004 OLE
MG0003 / (b) (6)	Placebo	MG crisis	23	1 (4 th infusion)	5	Severe SAE (unrelated)	Resolved with IVIg unchanged prednisone, pyridostigmine Withdrawn due to MG crisis. Enrolled in MG0004 OLE
MG0003 / (b) (6)	Placebo	MG worsening (two events: during double-blind treatment period and observation period)	22	7 (3 rd infusion) 57 (3 rd infusion)	3	Severe SAE (unrelated)	Resolved with IVIg Withdrawn due to MG worsening. No OLE. A second episode of MG worsening. Resolved in 2 days with IVIg
MG0003 / (b) (6)	RZ 10 mg/kg	MG exacerbation	76	39 (6 th and final infusion)	9	Severe SAE (unrelated)	Resolved. The MG worsening event (unspecified) occurred during the observation period after the sixth and last infusion in Study MG0003. Treated with IVIg. Discontinued the study during observation period due to MG worsening. Did not enroll into MG0004 or MG0007. Unchanged prednisone, pyridostigmine.
MG0003 / (b) (6)	RZ 10 mg/kg	MG worsening	53	18 (6 th and final infusion)	13	Severe SAE (unrelated)	Resolved. The MG worsening event (ptosis, double vision, dysarthria, fatigue while chewing, muscle weakness) occurred during the observation period after the sixth and last infusion in Study MG0003. Treated with IVIg. Completed the Study MG0003. Did not enroll into MG0004 or MG0007.
MG0003 / (b) (6) ^a	RZ 7 mg/kg	MG worsening (mild muscular weakness)	57	22 (5 th and final infusion)	N/A ongoing	Mild (unrelated)	Received IVIg and methylprednisolone 16 days after the symptom onset. Lost to follow up.

BLA 761286
Rystiggo (rozanolixizumab)

Subject ID	Study Arm	MedDRA PT	Time Between Onset and First Infusion (Days)	Time Between Onset and Last Infusion (Days)	Duration (Days)	Intensity (Relation to Study Drug)	Outcome
MG0003 / (b) (6)	RZ						
	≈7 mg/kg	MG exacerbation	3	3 (1 st infusion)	2	Severe SAE (vomiting related to study drug)	Resolved. The MG worsening event (dysarthria, ptosis, and shortness of breath) occurred after the first infusion in Study MG0003. No rescue therapy given. Treated for severe vomiting and aspiration pneumonia. No ventilation support. Unchanged pyridostigmine. Missed second dose of the study drug. Received 5 doses in the study. Enrolled into MG0007 OLE

Source: Module 5.3.5.1 MG0003-narratives and MG0003-listing-demog Table 2.3.1

^acase narrative provided in BLA761286\0010\Module 5.3.5.1\mg0003

Abbreviations: AZT, azathioprine; IVIG, immunoglobulin; MedDRA, Medical Dictionary for Regulatory Activities; MG, myasthenia gravis; NA, not applicable; OLE, open-label extension; PT, preferred term; RZ, rozanolixizumab; SAE, serious adverse event

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study MG0003

In Study MG0003, the frequency of TEAEs leading to treatment discontinuation was higher in the rozanolixizumab ≈ 10 mg/kg treatment group compared to rozanolixizumab ≈ 7 mg/kg and placebo groups ([Table 47](#), [Table 48](#)). A total of five subjects (7.2%) in the rozanolixizumab ≈ 10 mg/kg treatment group experienced TEAEs that led to treatment discontinuation including one subject who reported metastatic squamous cell carcinoma, oral herpes, and deep vein thrombosis; one subject experienced vomiting and upper abdominal pain; and one subject each reported diarrhea, tracheal device dislocation, and pruritus. In the rozanolixizumab ≈ 7 mg/kg dose group, one subject each experienced headache and arthralgia that led to treatment discontinuation. None of the subjects in the rozanolixizumab treatment groups discontinued treatment due to MG worsening/crisis, whereas two subjects on placebo withdrew from the Study MG0003.

Brief case summaries of TEAEs resulting in rozanolixizumab treatment discontinuation are provided below (source: Module 5.3.5.1. mg0003-narratives):

- Subject ID MG0003/[REDACTED] (b) (6) experienced nonserious AEs of upper abdominal pain and vomiting 4 days after the first rozanolixizumab ≈ 10 mg/kg SC infusion that led to treatment discontinuation. The event resolved 19 days after symptom onset. The AEs were considered moderate intensity. The subject did not have medical comorbidities or other etiologies which could have caused the AEs. Additionally, absence of the prior history of similar symptoms and the suggestive time to onset indicate that these AEs were likely related to rozanolixizumab.
- Subject ID MG0003/[REDACTED] (b) (6) experienced severe headache (ongoing neck sprain) and vomiting 3 days after the first rozanolixizumab ≈ 10 mg/kg SC infusion. There was no change in treatment. Headache resolved in 3 days. The subject reported mild pruritus 29 days after the first infusion and 8 days after fourth infusion that led to treatment discontinuation. The event resolved 15 days after onset. Given the suggestive time to onset and absence of other potential etiologies, the AEs of headache and pruritis were likely related to rozanolixizumab.
- Subject ID MG0003/[REDACTED] (b) (6) experienced grade 3 diarrhea 2 days after the first dose of rozanolixizumab ≈ 10 mg/kg SC infusion that led to treatment discontinuation. Other symptoms included fevers (38.3°C) and cramping abdominal pain. The etiology for diarrhea was not determined. The subject was admitted to a hospital and treated with natrium and a combination of fempiverinium with metamizole and pitofenone. The event was considered resolved. The suggestive time to onset, the absence of alternative etiologies, and no prior history of similar symptoms indicate that the adverse event (AE) of diarrhea was likely related to the rozanolixizumab.
- Subject ID MG0003/[REDACTED] (b) (6) experienced oral herpes, metastatic squamous cell carcinoma in the inguinal region and femoral vein thrombosis 26 days after the first and fourth day after the fourth rozanolixizumab ≈ 10 mg/kg SC infusion that led to treatment discontinuation. Because the subject had episodes of squamous cell carcinoma before enrolling into Study MG0003, the AE was unlikely related to rozanolixizumab.

- Subject ID MG0003/[REDACTED] (b) (6) experienced acute respiratory failure due to tracheal device dislocation in the setting of tracheostomy device dislocation, tracheal stenosis, and lobar pneumonia (SARS-COV-2 negative) 43 days after the first and seventh days after the last rozanolixizumab v10 mg/kg SC infusion that led to treatment discontinuation. Note that the subject missed fifth dose due to pyrexia and received a total of five infusions in Study MG0003. The subject had a tracheostomy for tracheal device dislocation, treated with antibiotics and did not require ventilatory assistance. The SAE resolved in 28 days from the onset. The device dislocation was unlikely related to rozanolixizumab.
- Subject ID MG0003/[REDACTED] (b) (6) experienced moderate joint pain 4 days after the first rozanolixizumab ≈ 7 mg/kg SC infusion. The subject was admitted to a hospital. The subject felt better on oral nonsteroidal anti-inflammatory medication and the joint pain resolved in 5 days. The subject had no previous history of joint pains. The subject experienced worsening joint pain and difficulty in walking 10 days after the first infusion and 2 days after the second infusion that led to treatment discontinuation. The subject was again admitted to a hospital and became a wheelchair bound. The event resolved 11 days after onset. The suggestive time to onset, the absence of alternative etiologies, and no prior history of similar symptoms indicate that the AE of joint pain was likely related to the rozanolixizumab.
- Subject ID MG0003/[REDACTED] (b) (6) experienced nonserious severe headache 4 days after the first rozanolixizumab ≈ 7 mg/kg SC infusion that led to treatment discontinuation. Other symptoms included pyrexia, photophobia, phonophobia, nausea, and vertigo. The event resolved 14 days after the onset. The subject had a past medical history of headaches and nausea before enrolling into Study MG0003. Given the suggestive time to onset the AE of severe headache was likely related to rozanolixizumab.

Table 47. Subjects With Adverse Events¹ Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study MG0003

Table System Organ Class Preferred Term	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ³	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ³	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ³
Any AE leading to discontinuation	2 (3.0)	2 (3.1)	0.1 (-5.8, 6.0)	5 (7.2)	4.3 (-3.1, 11.6)	7 (5.3)	2.3 (-3.3, 7.8)
Gastrointestinal disorders (SOC)	0	0	0 (0, 0)	2 (2.9)	2.9 (-1.1, 6.9)	2 (1.5)	1.5 (-0.6, 3.6)
Abdominal pain upper	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Diarrhea	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Vomiting	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Infections and infestations (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Oral herpes	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Arthralgia	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Metastatic squamous cell carcinoma	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Nervous system disorders (SOC)	2 (3.0)	1 (1.6)	-1.4 (-6.5, 3.7)	0	-3.0 (-7.1, 1.1)	1 (0.8)	-2.2 (-6.6, 2.1)
Headache	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Myasthenia gravis	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Myasthenia gravis crisis	1 (1.5)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)	0	-1.5 (-4.4, 1.4)
Product issues (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Device dislocation	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Skin and subcutaneous tissue disorders (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Pruritus	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Vascular disorders (SOC)	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Deep vein thrombosis	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.³Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab; SOC, system organ class

Table 48. Subjects With Adverse Events¹ Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study MG0003²

System Organ Class (SOC) FMQ (Narrow) ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ⁴
Gastrointestinal disorders (SOC)							
Abdominal Pain	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Diarrhea	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Dyspepsia	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Vomiting	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Infections and infestations (SOC)							
Viral Infection	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Musculoskeletal and connective tissue disorders (SOC)							
Arthralgia	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Nervous system disorders (SOC)							
Headache	0	1 (1.6)	1.6 (-1.5, 4.6)	0	0 (0, 0)	1 (0.8)	0.8 (-0.7, 2.2)
Skin and subcutaneous tissue disorders (SOC)							
Pruritus	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Vascular disorders (SOC)							
Thrombosis	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)
Thrombosis Venous	0	0	0 (0, 0)	1 (1.4)	1.4 (-1.4, 4.3)	1 (0.8)	0.8 (-0.7, 2.2)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.³Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

⁴Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.

Abbreviations: FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab.; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Study MG0003

[Table 49](#) lists the TEAEs in Study MG0003 with a cutoff frequency of at least 5% in the either rozanolixizumab arm and higher frequency than placebo consistent with the cutoffs used in labeling for efgartigimod, eculizumab, and ravulizumab, the monoclonal antibodies approved for the indication of anti-AChR antibody seropositive MG.

The most frequently reported TEAEs in Study MG0003 in rozanolixizumab treated subjects were headache, diarrhea, pyrexia, and infections including upper respiratory tract infections and herpes simplex. Injection site reactions were seen in 9% of the subjects in rozanolixizumab treated group compared to 3% in the placebo group. Infections and headaches were a topic of special interest for this review and are discussed further in [Section 7.7.1](#) and [Section 7.7.2](#) respectively. Other frequent TEAEs for potential labeling included nausea, vomiting, musculoskeletal pain, and skin rash. Hypersensitivity reactions and administration site reactions, and gastrointestinal disorders are discussed in [Section 7.7.3](#) and [Section 7.7.4](#) respectively.

The TEAE of hypertension was reported in six (4.5%) subjects treated with rozanolixizumab; however, four subjects had a pre-existing hypertension. The reviewer notes that hypertension was the most common medical comorbidity in the subjects upon entry to Study MG0003 (31.5%; [Table 17](#)). Hypertension was not likely related to the use of rozanolixizumab.

Table 49. Treatment-Emergent Adverse Events¹ in ≥5% of the Subjects Treated With Rozanolixizumab and More Frequently Than Placebo Group, Safety Population, Study MG0003²

Preferred Term ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ≈10 mg/kg N=69 n (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI) ⁴	RLZ Total N=133 n (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI) ⁴
Any AE	45 (67.2)	52 (81.2)	14.1 (-0.7, 28.8)	57 (82.6)	15.4 (1.1, 29.8) *	109 (82.0)	14.8 (1.8, 27.8) *
Headache ⁵	13 (19.4)	31 (48.4)	29 (13.6, 44.5) *	28 (40.6)	21.2 (6.2, 36.1) *	59 (44.3)	24.9 (12.3, 37.6) *
Diarrhea	9 (13.4)	16 (25.0)	11.6 (-1.8, 25.0)	11 (15.9)	2.5 (-9.4, 14.4)	27 (20.3)	6.9 (-3.8, 17.5)
Pyrexia ⁶	1 (1.5)	8 (12.5)	11.0 (2.4, 19.6) *	15 (21.7)	20.2 (10.1, 30.4) *	23 (17.3)	15.8 (8.7, 22.9) *
Nausea	5 (7.5)	5 (7.8)	0.3 (-8.8, 9.5)	8 (11.6)	4.1 (-5.7, 14.0)	13 (9.8)	2.3 (-5.8, 10.4)
Injection site reaction ⁷	2 (3.0)	6 (9.4)	6.4 (-1.8, 14.6)	6 (8.7)	5.7 (-2.1, 13.5)	12 (9.0)	6.0 (-0.3, 12.4)
Upper respiratory tract infection ⁸	4 (6.0)	3 (4.7)	-1.3 (-9.0, 6.4)	8 (11.6)	5.6 (-3.8, 15.1)	11 (8.3)	2.3 (-5.1, 9.7)
Abdominal pain ⁹	4 (6.0)	6 (9.4)	3.4 (-5.7, 12.5)	5 (7.2)	1.3 (-7.1, 9.6)	11 (8.3)	2.3 (-5.1, 9.7)
Arthralgia	2 (3.0)	4 (6.2)	3.3 (-3.9, 10.5)	5 (7.2)	4.3 (-3.1, 11.6)	9 (6.8)	3.8 (-2.1, 9.7)
Myalgia	1 (1.5)	2 (3.1)	1.6 (-3.5, 6.8)	4 (5.8)	4.3 (-1.9, 10.5)	6 (4.5)	3.0 (-1.5, 7.6)
Rash ¹⁰	2 (3.0)	4 (6.2)	3.3 (-3.9, 10.5)	5 (7.2)	4.3 (-3.1, 11.6)	9 (6.8)	3.8 (-2.1, 9.7) *
Vomiting	1 (1.5)	2 (3.1)	1.6 (-3.5, 6.8)	4 (5.8)	4.3 (-1.9, 10.5)	6 (4.5)	3.0 (-1.5, 7.6)
Hypertension ¹¹	0	5 (7.8)	7.8 (1.2, 14.4) *	1 (1.4)	1.4 (-1.4, 4.3)	6 (4.5)	4.5 (1.0, 8.0) *
Herpes simplex ¹²	0	0	0 (0, 0)	4 (5.8)	5.8 (0.3, 11.3)	4 (3.0)	3.0 (0.1, 5.9)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

³Coded as MedDRA preferred terms.

⁴Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo.

⁵includes headache and migraine (n=2 each in rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively)

⁶includes pyrexia and hyperthermia

⁷includes Injection site reaction, rash, erythema, inflammation, urticaria and discomfort, and infusion site bruising, pain and erythema, and application site erythema and pruritis

⁸includes upper respiratory tract infection, rhinitis, sinusitis, and nasopharyngitis

⁹includes abdominal discomfort, abdominal pain upper, and flank pain

¹⁰includes rash, papular rash, and rash erythematous

¹¹includes hypertension and hypertensive crisis (n=1 in rozanolixizumab ≈10 mg/kg group)

¹²includes oral herpes and herpes simplex

*potential imbalance between rozanolixizumab and placebo groups

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab.

7.6.2.6. Laboratory Findings, Study MG0003

Hematology

The reviewer did not identify a safety signal for abnormal hematology laboratory findings in subjects treated with rozanolixizumab in Study MG0003. In Study MG0003, the most frequent postbaseline abnormalities were decreased leukocytes, decreased neutrophils, and decreased platelet counts in the subjects receiving rozanolixizumab ([Table 50](#)). The laboratory abnormalities of decreased platelets and decreased leukocytes counts had similar maximum lowest values between rozanolixizumab and placebo arms. The maximum lowest platelet count was $114 \times 10^9/L$ on day 8 and day 36 in the rozanolixizumab ≈ 10 mg/kg group compared to placebo $121 \times 10^9/L$ on day 8 and day 43 during the treatment period (reference range 150 to $400 \times 10^9/L$). The maximum lowest leukocytes count was $2.13 \times 10^9/L$ on day 36 in the rozanolixizumab ≈ 10 mg/kg group compared to placebo $2.19 \times 10^9/L$ on day 43 during the treatment period (reference range 3.8 to $10.7 \times 10^9/L$). One subject in the rozanolixizumab ≈ 7 mg/kg group had the lowest leukocyte count $1.8 \times 10^9/L$ on day 99 the end of the observation period in Study MG0003.

One subject experienced neutropenia (less than $1.0 \times 10^9/L$) in the rozanolixizumab ≈ 10 mg/kg group during the treatment period. The maximum lowest neutrophils count was $0.68 \times 10^9/L$ on day 36 in the rozanolixizumab ≈ 10 mg/kg group compared to placebo $1.05 \times 10^9/L$ on day 43 during the treatment period (reference range 2.0 to 7.2 to $10.7 \times 10^9/L$).

The proportion of subjects with outlier values of decreased leukocytes, decreased neutrophils, and decreased platelets counts was balanced between rozanolixizumab and placebo groups ([Table 51](#)). More subjects in the rozanolixizumab ≈ 10 mg/kg group had elevated leukocytes counts than rozanolixizumab ≈ 7 mg/kg and placebo groups.

Change From Baseline in Hematology Laboratory Parameters

The subjects receiving rozanolixizumab had a decrease from baseline in the mean leukocytes, neutrophils and platelets counts compared to placebo during the treatment period. The mean decrease in leukocytes, decrease in neutrophils, and decrease in platelets were observed from day 8 (i.e., the first postbaseline assessment) and the levels returned to either baseline or comparable to placebo by day 99 the end of the observation period in Study MG0003. The incidence of normal to low shifts from baseline in leukocytes, neutrophils and platelets counts was similar between rozanolixizumab and placebo groups ([Table 52](#)).

The mean changes from baseline in lymphocytes, eosinophils and hemoglobin levels, and prothrombin time were comparable to placebo and not clinically significant. The activated partial thromboplastin time levels were not assessed during the treatment period and the sample sizes were smaller during later visits in the observation period.

Table 50. Mean Blood Cell Count Change From Baseline to Postbaseline, Safety Population, Study MG0003

Mean Change From Baseline to Day 43	Placebo N=67	RLZ≈7 mg/kg N=64	RLZ≈10 mg/kg N=69
WBC (x10 ⁹ /L)	-0.03	-0.50	-0.37
Neutrophils (x10 ⁹ /L)	-0.08	-0.45	-0.41
Platelets (x10 ⁹ /L)	6.1	-6.6	-20.0

Source: ad b.xpt; Software: R

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: N, number of subjects in treatment arm, RLZ, rozanolixizumab; WBC, white blood cells

Table 51. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study MG0003

Laboratory Parameter	Placebo (N=67) n (%)	Rozanolixizumab ≈7 mg/kg (N=64) n (%)	Rozanolixizumab ≈10 mg/kg (N=69) n (%)
WBC, low (cells/uL)			
Level 1 (<3500)	8 (11.9)	6 (9.4)	7 (10.1)
Level 2 (<3000)	3 (4.5)	2 (3.1)	3 (4.3)
Level 3 (<1000)	0	0	0
WBC, high (cells/uL)			
Level 1 (>10800)	13 (19.4)	12 (18.8)	19 (27.5)
Level 2 (>13000)	4 (6.0)	2 (3.1)	7 (10.1)
Level 3 (>15000)	3 (4.5)	0	6 (8.7)
Neutrophils, low (cells/uL)			
Level 1 (<2000)	10 (14.9)	9 (14.1)	10 (14.5)
Level 2 (<1000)	0	0	1 (1.4)
Level 3 (<500)	0	0	0
Lymphocytes, low (cells/uL)			
Level 1 (<1000)	28 (41.8)	19 (29.7)	26 (37.7)
Level 2 (<750)	16 (23.9)	9 (14.1)	18 (26.1)
Level 3 (<500)	6 (9.0)	4 (6.2)	7 (10.1)
Lymphocytes, high (cells/uL)			
Level 1 (>4000)	2 (3.0)	0	2 (2.9)
Level 2 (>10000)	0	0	0
Level 3 (>20000)	0	0	0
Platelets, low (cells/uL)			
Level 1 (<140000)	3 (4.5)	2 (3.1)	4 (5.8)
Level 2 (<125000)	2 (3.0)	0	2 (2.9)
Level 3 (<100000)	0	0	0
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	6 (9.0)	8 (12.5)	4 (5.8)
Level 3 (>2 g/dL dec. from baseline)	4 (6.0)	3 (4.7)	1 (1.4)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	3 (4.5)	3 (4.7)	0
Level 3 (>3 g/dL inc. from baseline)	0	0	0

Source: ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal; WBC, white blood cells

Table 52. Hematology Laboratory Data Shifts From Baseline To Postbaseline, Safety Population, Study MG0003

Laboratory Parameter Shift from Baseline	Placebo (N=67) n/Nw (%)	Rozanolixizumab ≈7 mg/kg (N=64) n/Nw (%)	Rozanolixizumab ≈10 mg/kg (N=69) n/Nw (%)
Leukocytes (10 ⁹ /L)			
Normal to High	6/67 (9)	5/64 (7.8)	5/69 (7.2)
Normal to Low	5/67 (7.5)	3/64 (4.7)	6/69 (8.7)
Normal to Missing	7/67 (10.4)	9/64 (14.1)	9/69 (13)
Neutrophils (10 ⁹ /L)			
Normal to High	10/67 (14.9)	5/64 (7.8)	11/69 (15.9)
Normal to Low	5/67 (7.5)	2/64 (3.1)	4/69 (5.8)
Normal to Missing	5/67 (7.5)	10/64 (15.6)	9/69 (13)
Lymphocytes (10 ⁹ /L)			
Normal to High	2/67 (3)	0/64 (0)	2/69 (2.9)
Normal to Low	15/67 (22.4)	9/64 (14.1)	14/69 (20.3)
Normal to Missing	6/67 (9)	10/64 (15.6)	8/69 (11.6)
Platelets (10 ⁹ /L)			
Normal to High	4/67 (6)	1/64 (1.6)	4/69 (5.8)
Normal to Low	4/67 (6)	2/64 (3.1)	2/69 (2.9)
Normal to Missing	9/67 (13.4)	9/64 (14.1)	9/69 (13)
Hematocrit (%)			
Normal to High	7/67 (10.4)	5/64 (7.8)	3/69 (4.3)
Normal to Low	3/67 (4.5)	4/64 (6.2)	3/69 (4.3)
Normal to Missing	7/67 (10.4)	9/64 (14.1)	7/69 (10.1)

Source: ad b.xpt; Software: R

Duration is from day 1 to day 43.

Abbreviations: n, number of patients meeting criteria; N, number of subjects in treatment arm; Nw, number of patients with data

Chemistry

Decrease in Serum Albumin Levels

The most frequent abnormal postbaseline chemistry laboratory findings were decreased serum albumin values in the subjects receiving rozanolixizumab. The maximum lowest albumin value (2.9 g/dL) was observed in one subject receiving rozanolixizumab $\approx$ 10 mg/kg at day 99 which was the last day in the observation period. Please see Section [7.7.5](#) for the discussion of low albumin levels as a key safety review issue of special interest.

Change From Baseline in Serum Albumin Levels

The mean decrease from baseline at day 43 in serum albumin levels was -2.2 g/L in the rozanolixizumab $\approx$ 7 mg/kg group and -2.3 g/L in the rozanolixizumab $\approx$ 10 mg/kg group compared with -0.45 g/L in the placebo group during the treatment period in Study MG0003. The decreases in albumin values in the rozanolixizumab treated subjects were observed as early as day 8 which was the first postbaseline visit in Study MG0003. The mean albumin values in the rozanolixizumab treated subjects remained persistently lower than placebo throughout the treatment period and resolved to the placebo levels on day 71 during the observation period in Study MG0003.

Increase in Fasting Blood Glucose Level

More subjects in the rozanolixizumab $\approx$ 10 mg/kg group had increased postbaseline fasting glucose values ($\geq$ 100 to 125) compared to the rozanolixizumab $\approx$ 7 mg/kg and placebo groups (32.7% vs. 22.9% and 23.5%, respectively). One subject with increased fasting glucose levels 5.97 mmol/L at baseline in the rozanolixizumab $\approx$ 10 mg/kg group reported two TEAEs related to abnormal fasting glucose values during the treatment period with the maximum highest glucose value 6.13 mmol/L on day 36 and 6.16 mmol/L on day 43 (normal reference 4.1 to 5.5 mmol/L; source: clinical study report (CSR) MG0003 page 216; by subject listing 8.1.2). One subject with increased fasting glucose levels 5.97 mmol/L at baseline in the rozanolixizumab $\approx$ 10 mg/kg group reported two TEAEs related to abnormal fasting glucose values during the treatment period with the maximum highest glucose value 6.13 mmol/L on day 36 and 6.16 mmol/L on day 43 (normal reference 4.1 to 5.5 mmol/L; source: clinical study report (CSR) MG0003 page 216; by subject listing 8.1.2).

Change From Baseline in Fasting Blood Glucose Level

There were minimal and clinically nonsignificant changes from baseline to day 43 in the mean glucose levels -0.21 mmol/L in the rozanolixizumab $\approx$ 10 mg/kg group during the treatment period compared to 0.20 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg group and placebo groups.

Serum Electrolytes

There were no reported TEAEs related to serum electrolyte laboratory values. One subject in the rozanolixizumab 10 mg/kg group experienced the maximum lowest sodium levels 117 mEq/L on day 99 the last day in the observation period. None of the subjects had abnormally high sodium levels ($>$ 150 mEq/L). The maximum lowest and highest potassium values were 3.3 mEq/L and 5.6 mEq/L on day 43 in the rozanolixizumab $\approx$ 10 mg/kg group. The proportions of subjects with

abnormal low potassium levels (<3.6 mEq/L) were similar between rozanolixizumab and placebo groups. Relatively more subjects in the rozanolixizumab ≈ 7 mg/kg group had abnormal low corrected calcium levels (<8.4 and >8) compared with the rozanolixizumab ≈ 10 mg/kg and placebo groups (28.1% vs. 20.3% and 9%, respectively). The maximum lowest calcium levels were 1.95 mmol/L (7.8 mg/dL; normal reference 8.5 to 10.2 mg/dL) on day 22 during the treatment period in the rozanolixizumab ≈ 7 mg/kg group.

Change From Baseline in Serum Electrolytes

The mean changes from baseline to day 43 in serum sodium, potassium, and corrected calcium levels were minimal and clinically nonsignificant in the subjects receiving rozanolixizumab in Study MG0003. The mean changes from baseline to day 43 in serum sodium, potassium, and corrected calcium levels were minimal and clinically nonsignificant in the subjects receiving rozanolixizumab in Study MG0003.

Blood Urea Nitrogen

The proportion of subjects with elevated blood urea nitrogen (BUN) values was higher in the rozanolixizumab treated groups compared with placebo in Study MG0003 (21.1% vs. 17.9%). The maximum highest BUN values were 14.8 mmol/L on day 8 and 14.2 mmol/L on day 99 which was the last observation day in the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups, respectively compared with placebo 10.5 mmol/L on day 71 during observation period in Study MG0003 (normal reference generally 2.1 to 8.5 mmol/L). Note that the interpretation of BUN values is dependent on the age and sex. There were no reported TEAEs related to BUN levels. None of the rozanolixizumab treated subjects in Study MG0003 had abnormal high creatinine values (see kidney function [Table 54](#)).

Change From Baseline in BUN Levels

The mean changes from baseline to day 43 in BUN values were minimal and clinically nonsignificant during the treatment period in rozanolixizumab subjects compared with placebo in Study MG0003.

Lipid Panel

The reviewer did not identify a safety signal for abnormal LDL or other lipids in subjects treated with rozanolixizumab in Study MG0003. This finding agrees with the absence of a safety signal for elevated LDL or other lipids in subjects treated with efgartigimod, a previously approved FcRn blocker drug for the treatment of anti-AChR-gMG. Note that cholesterol levels were reviewed as an adverse event special interest for efgartigimod because elevated LDL cholesterol levels led to premature termination of a phase 2 study (NCT03938545) after 12 weeks of treatment with RVT-1401, a human anti-FcRn monoclonal antibody for the treatment of subjects with Graves' ophthalmopathy ([Men et al. 2021](#)).

The nonfasted monitoring of lipids was introduced in protocol amendment 4 of Study MG0003 (Feb 23, 2021) and in protocol amendment 1 of MG0007 (Mar 03, 2021). Lipids analyte data were available in 53% of the subjects in the rozanolixizumab ≈ 7 mg/kg and rozanolixizumab ≈ 10 mg/kg groups, and 58% of the subjects in the placebo group. The Applicant states that the blood samples were collected during nonfasting conditions.

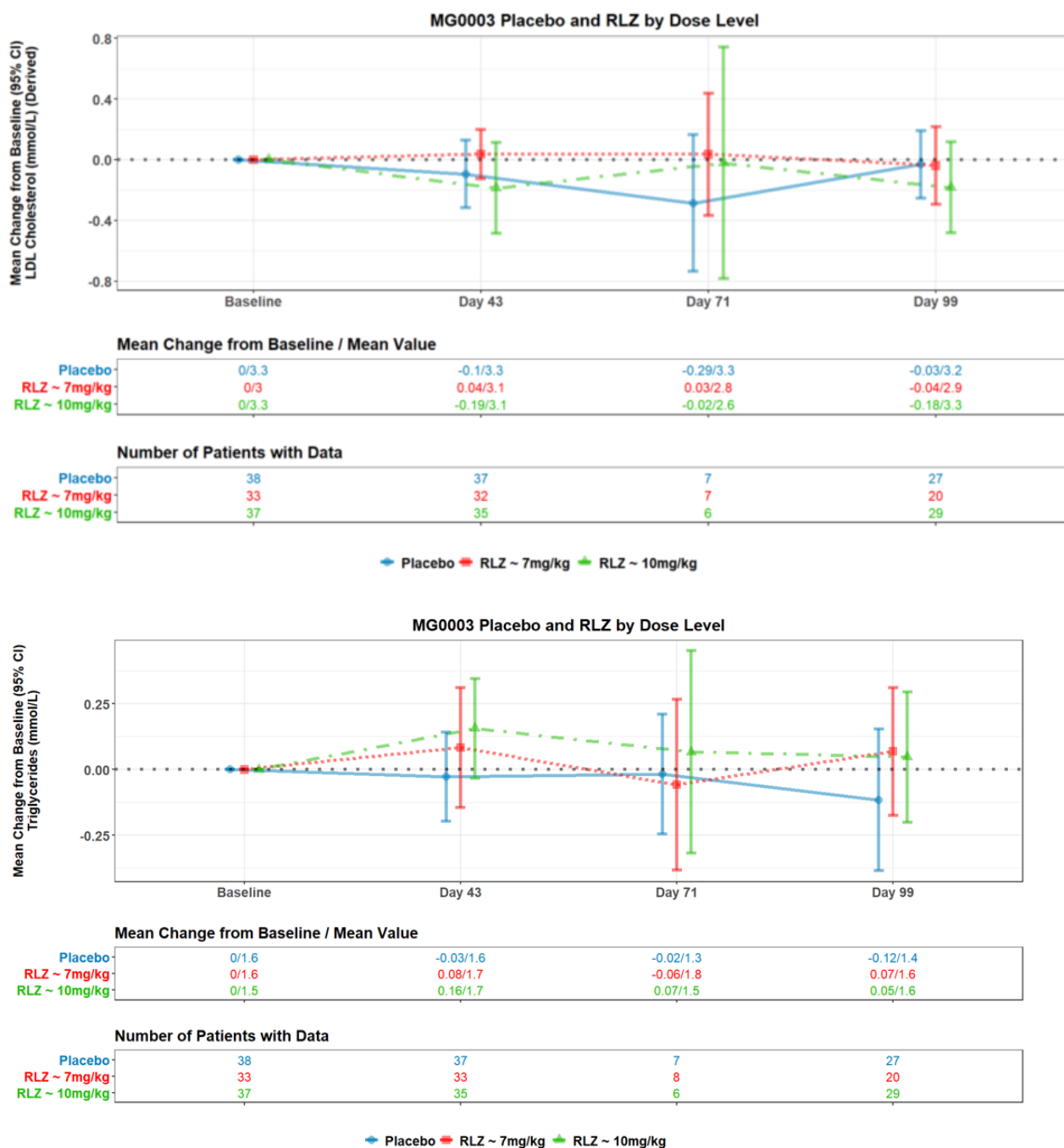
The proportion of subjects with outlier LDL cholesterol and triglycerides values was similar among treatment groups ([Table 53](#)). More female subjects receiving rozanolixizumab had lower high-density lipoprotein (HDL) cholesterol levels compared to placebo, but the sample size was small. This difference was not apparent in smaller sample size of male subjects.

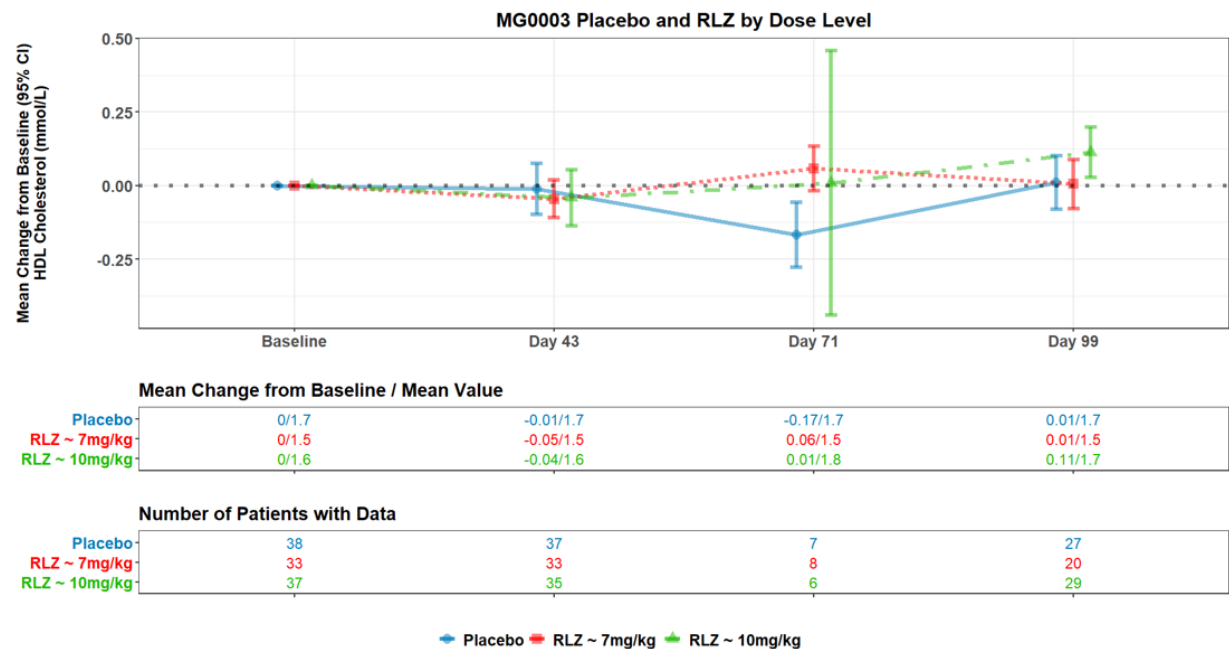
The maximum highest LDL cholesterol levels on day 43 were similar among treatment groups: 4.47 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg group, 5.96 mmol/L in the rozanolixizumab $\approx$ 10 mg/kg group, and 5.83 mmol/L in the placebo group (reference <2.6 mmol/L). The maximum lowest HDL cholesterol levels on day 43 were similar among treatment groups: 0.90 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg group, 0.79 mmol/L in the rozanolixizumab $\approx$ 10 mg/kg group, and 0.86 mmol/L in the placebo group (reference >1.55 mmol/L).

Change From Baseline

The changes from baseline in LDL cholesterol, HDL cholesterol, and triglyceride levels in rozanolixizumab treated subjects were minimal and not clinically significant compared to placebo ([Figure 7](#)). The mean change from baseline in LDL cholesterol at day 43 was 0.04 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg group, -0.19 mmol/L in the rozanolixizumab $\approx$ 10 mg/kg group and -0.1 mmol/L in the placebo group ([Figure 7](#)). The mean change from baseline in triglycerides at day 43 was 0.08 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg group, 0.16 mmol/L in the rozanolixizumab $\approx$ 10 mg/kg group and -0.03 mmol/L in the placebo group. The mean change from baseline in HDL cholesterol levels on day 43 was -0.05 mmol/L, -0.04 mmol/L and -0.01 mmol/L in the rozanolixizumab $\approx$ 7 mg/kg, rozanolixizumab $\approx$ 10 mg/kg, and placebo groups respectively ([Figure 7](#)).

Figure 7. Mean Lipids Levels Change From Baseline Over Time, Safety Population, Study MG0003





Source: ad b.xpt; Software: R.
Note: Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; RLZ, rozanolixizumab

Table 53. Subjects With One or More Lipid's Analyte Values Exceeding Specified Levels, Safety Population, Study MG0003

Laboratory Parameter	Placebo (N=67) n/Nw (%)	Rozanolixizumab ≈7 mg/kg (N=64) n/Nw (%)	Rozanolixizumab ≈10 mg/kg (N=69) n/Nw (%)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	26/39 (66.7)	17/34 (50.0)	24/37 (64.9)
Level 2 (>210)	23/39 (59.0)	15/34 (44.1)	22/37 (59.5)
Level 3 (>225)	19/39 (48.7)	12/34 (35.3)	20/37 (54.1)
LDL cholesterol, high (mg/dL)			
Level 1 (>130)	19/39 (48.7)	15/33 (45.5)	17/37 (45.9)
Level 2 (>160)	10/39 (25.6)	8/33 (24.2)	10/37 (27.0)
Level 3 (>190)	2/39 (5.1)	0/33 (0)	2/37 (5.4)
Triglycerides, high (mg/dL)			
Level 1 (>150)	16/39 (41.0)	14/34 (41.2)	17/37 (45.9)
Level 2 (>300)	3/39 (7.7)	5/34 (14.7)	3/37 (8.1)
Level 3 (>500)	0/39 (0)	0/34 (0)	0/37 (0)
HDL cholesterol, males, low (mg/dL)			
Level 1 (<40)	3/11 (27.3)	3/17 (17.6)	3/15 (20.0)
Level 2 (<30)	0/11 (0)	0/17 (0)	0/15 (0)
Level 3 (<20)	0/11 (0)	0/17 (0)	0/15 (0)
HDL cholesterol, females, low (mg/dL)			
Level 1 (<50)	5/28 (17.9)	7/17 (41.2)	6/22 (27.3)
Level 2 (<40)	1/28 (3.6)	1/17 (5.9)	2/22 (9.1)
Level 3 (<20)	0/28 (0)	0/17 (0)	0/22 (0)

Source: ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Kidney Function

Subjects with renal impairment defined as glomerular filtration rate (GFR) less than 45 mL/min/1.73m² were not enrolled in Study MG0003. None of the subjects receiving rozanolixizumab had abnormal high creatinine levels during Study MG0003 ([Table 54](#)). One subject each in the rozanolixizumab 7 mg/kg and 10 mg/kg groups had decreased GFR (≥25%) in postbaseline values.

No subjects had severe or serious TEAEs related to renal impairment. Three subjects (4.3%) with already low eGFR and elevated serum creatinine at baseline in the rozanolixizumab ≈10 mg/kg group had TEAEs of renal impairment (source: CSR Section 11.8.9 and case narratives in response to IR, eCTD Seq number 0013):

- [Subject ID MG0003/ \(b\) \(6\)](#): 76-year-old male subject randomized to rozanolixizumab ≈10 mg/kg dose with a medical history of hypertension, diabetes mellitus type 2, and overweight experienced a decrease in estimated glomerular filtration rate (eGFR) from 53.2 mL/min/1.73m² at baseline to 41.7 mL/min/1.73m² on day 71 (36 days after the final sixth infusion) during observation period. Serum creatinine 114.6 mmol/L was elevated at baseline and most of the time throughout the study (normal range, 64 to 104 mmol/L). Risk factors for kidney disease in the medical history of the subject included diabetes mellitus type 2 and hypertension, and concomitant medications such as

candesartan/hydrochlorothiazide and metformin. The event was considered nonserious moderate intensity TEAE which was not resolved during the study. Because the subject had impaired renal function upon study entry and the presence of alternative potential etiologies such as other medical comorbidities and medications, the renal impairment was unlikely related to rozanolixizumab.

- Subject ID MG0003/ (b) (6): 81-year-old male subject experienced a decrease in estimated glomerular filtration rate (eGFR) from 60.0 mL/min/1.73m² at baseline to 40.2 mL/min/1.73m² day 43 a week after the sixth and final dose of rozanolixizumab ≈10 mg/kg SC infusion. Serum creatinine 100.7 mmol/L and BUN 9.8 mmol/L were mildly elevated at baseline and most of the time throughout the study (normal range, creatinine 64 to 104 mmol/L and BUN 3 to 9.2 mmol/L). Risk factors for kidney disease in the medical history of the subject included hypertension and concomitant medications such as ramipril and furosemide. The subject also had an extensive medical and procedural history related to cardiovascular disease. He completed the observation period and rolled over to OLE Study MG0007. The event was considered nonserious mild intensity TEAE unrelated to rozanolixizumab which was not resolved during the study. Because the subject had impaired renal function upon study entry and the presence of alternative potential etiologies such as other medical comorbidities and medications, the renal impairment was unlikely related to rozanolixizumab.
- Subject ID MG0003/ (b) (6): 58-year-old female subject randomized to rozanolixizumab 10 mg/kg dose experienced a decrease in estimated glomerular filtration rate (eGFR) from 54.5 mL/min/1.73m² at baseline to 41.4 mL/min/1.73m² on day 8 one day after the second rozanolixizumab ≈10 mg/kg SC infusion during treatment period. The eGFR was 81.6 mL/min/1.73m² on day 22. Serum creatinine 98.4 mmol/L and BUN 11.7 mmol/L (normal range, creatinine 49 to 90 mmol/L and BUN 3.5 to 7.2 mmol/L) were elevated at baseline and most of the time throughout the study but returned to normal by day 43. Risk factors for kidney disease in the medical history of the subject included hypertension and concomitant medications such as tacrolimus and rosuvastatin. The subject continued to receive rozanolixizumab 10 mg/kg SC infusion weekly and received a total of five infusions in Study MG0003. She completed the observation period and enrolled into OLE Study MG0007. The event was considered nonserious moderate intensity TEAE which was not resolved during the Study. Because the subject had impaired renal function upon study entry and the presence of alternative potential etiologies such as other medical comorbidities and medications, the renal impairment was unlikely related to rozanolixizumab.

Change from Baseline

The mean changes from baseline to day 43 in the creatinine and eGFR levels were minimal and clinically nonsignificant during the treatment period in Study MG0003 ([Figure 8](#) and [Figure 9](#)).

Table 54. Subjects With One or More Kidney Function Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study MG0003

Laboratory Parameter	Placebo (N=67)	Rozanolixizumab ≈7 mg/kg (N=64)	Rozanolixizumab ≈10 mg/kg (N=69)
	n/Nw (%)	n/Nw (%)	n/Nw (%)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	2/67 (3.0)	0/63 (0)	0/69 (0)
Level 2 (≥2X baseline)	0/67 (0)	0/63 (0)	0/69 (0)
Level 3 (≥3X baseline)	0/67 (0)	0/63 (0)	0/69 (0)
eGFR, low (ml/min/1.73 m ²)			
Level 1 (≥25% decrease)	0/47 (0)	1/45 (2.2)	1/48 (2.1)
Level 2 (≥50% decrease)	0/47 (0)	0/45 (0)	0/48 (0)
Level 3 (≥75% decrease)	0/47 (0)	0/45 (0)	0/48 (0)

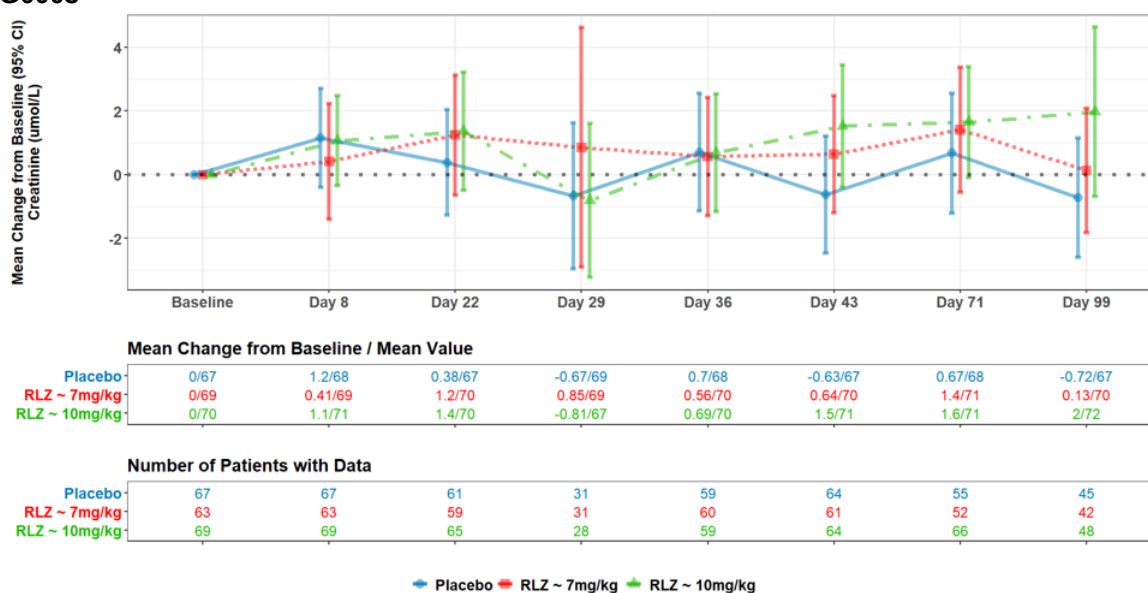
Source: ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

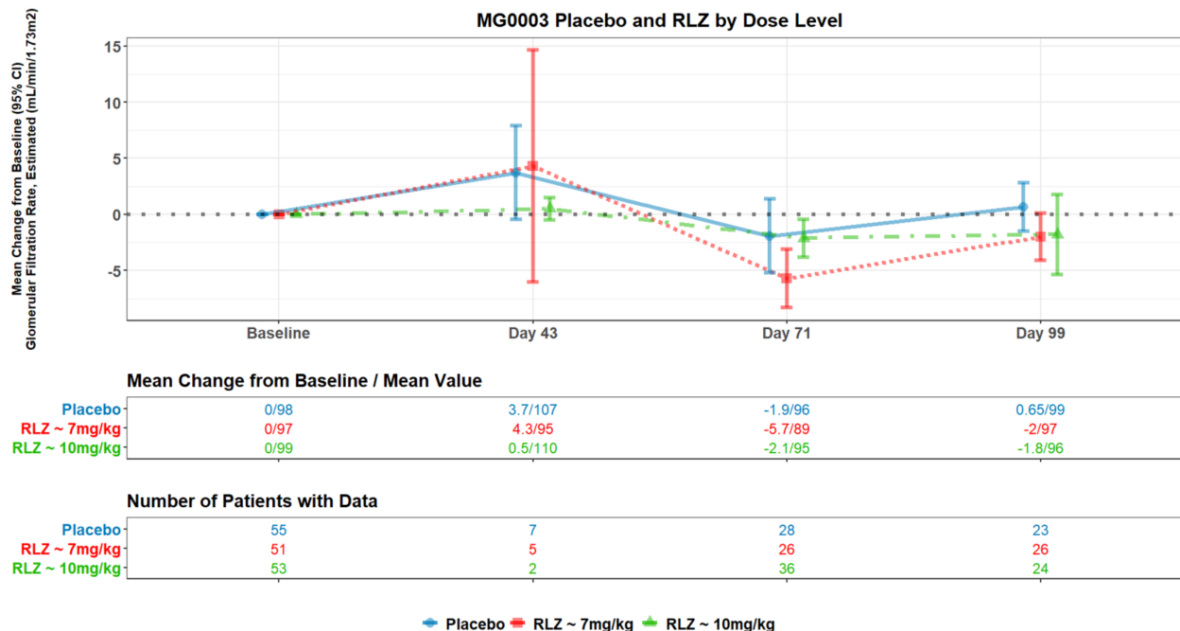
Figure 8. Mean Creatinine Levels Change From Baseline Over Time, Safety Population, Study MG0003



Source: ad b.xpt; Software: R.

Abbreviations: RLZ, rozanolixizumab

Figure 9. Mean Glomerular Filtration Rate (GFR) Change From Baseline Over Time, Safety Population, Study MG0003



Source: ad b.xpt; Software: R

Note: Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.

Abbreviations: RLZ, rozanolixizumab

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study MG0003

There were no serious drug-related hepatic disorders, liver function test (LFT) elevations meeting protocol-defined withdrawal criteria, or potential Hy's law cases ([Figure 10](#)) in Study MG0003.

[Table 55](#) shows the frequency of maximum postbaseline values meeting cut points above the upper limit of normal (ULN) for liver enzymes and bilirubin in the subjects treated with rozanolixizumab compared with placebo.

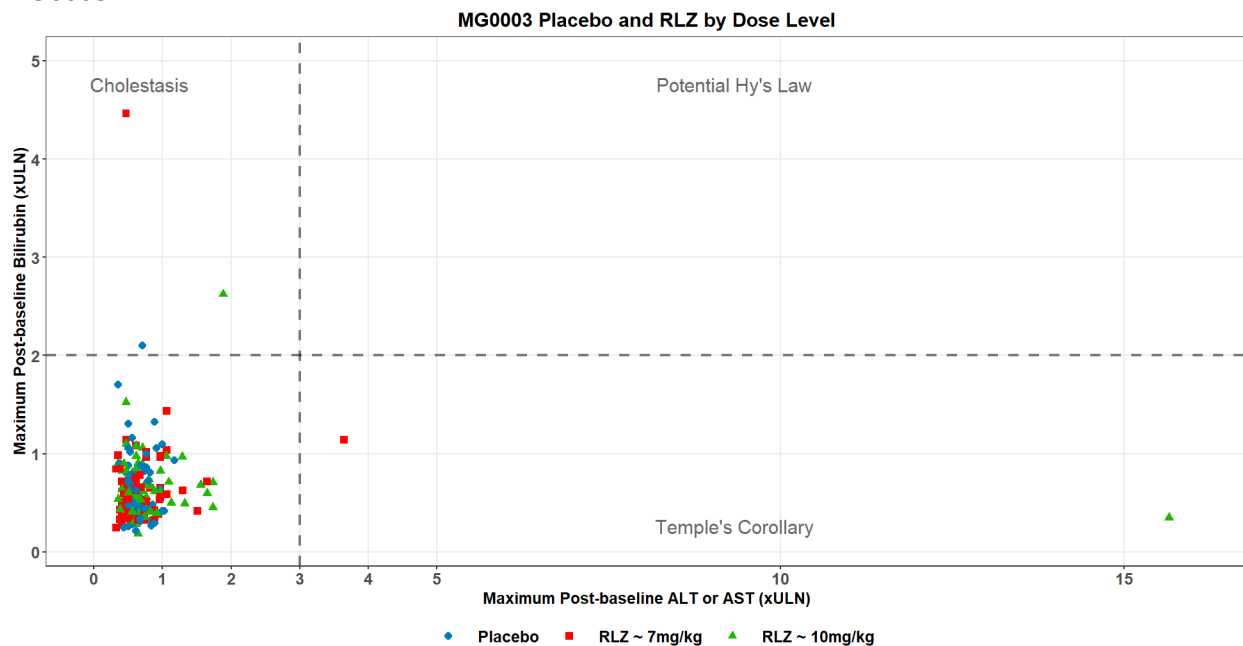
Three (2.2%) subjects receiving rozanolixizumab had abnormal LFT elevations during the treatment period in Study MG0003. All of them had their respective LFT values above ULN at the baseline visit. In the rozanolixizumab ≈ 7 mg/kg group, one subject with a medical history of increased liver enzymes experienced an elevated aspartate aminotransferase (AST) and alkaline phosphatase (ALP) and a nonserious TEAEs of mild hepatic fibrosis and nonalcoholic fatty liver disease. Two subjects with increased bilirubin levels at baseline in the rozanolixizumab ≈ 10 mg/kg group experienced elevated bilirubin levels and resolved. Because these subjects had impaired liver function upon study entry, the AEs were not likely related to rozanolixizumab.

Two additional subjects had LFT elevations during the last week of the observation period (8 weeks after the last dose) in Study MG0003 including one subject in the rozanolixizumab ≈ 10 mg/kg group who had elevated AST $>10\times$ ULN and alanine aminotransferase $>10\times$ ULN, and one subject in the rozanolixizumab ≈ 7 mg/kg group who had an elevated total bilirubin with a

medical history of Gilbert's syndrome. Given that these events occurred outside of the anticipated five drug half-lives period, the AEs were unlikely related to rozanolixizumab.

The postbaseline assessments of prothrombin time (PT) in the subjects receiving rozanolixizumab were limited by small sample size during the treatment period (n=6 and n=1 in the rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg groups, respectively versus n=7 in the placebo group). All abnormal PT values (>1.1 XULN) were observed during the observation period; all but one subject had abnormally elevated PT values at baseline and therefore unlikely related to rozanolixizumab.

Figure 10. Hepatocellular Drug-induced Liver Injury Screening Plot, Safety Population, Study MG0003



Source: ad b.xpt; Software: R.

Note: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

Note: A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RLZ, rozanolixizumab; ULN, upper limit of normal

Table 55. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study MG0003

Laboratory Parameter	Placebo (N=67) n/Nw (%)	Rozanolixizumab ≈7 mg/kg (N=64) n/Nw (%)	Rozanolixizumab ≈10 mg/kg (N=69) n/Nw (%)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	0/67	0/64	1/69 (1.4)
Level 2 (>5X ULN)	0/67	0/64	1/69 (1.4)
Level 3 (>10X ULN)	0/67	0/64	1/69 (1.4)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	0/67	1/64 (1.6)	1/69 (1.4)
Level 2 (>5X ULN)	0/67	0/64	1/69 (1.4)
Level 3 (>10X ULN)	0/67	0/64	1/69 (1.4)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	1/67 (1.5)	1/64 (1.6)	0/69
Level 2 (>2X ULN)	0/67	1/64 (1.6)	0/69
Level 3 (>3X ULN)	0/67	0/64	0/69
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	2/67 (3.0)	1/64 (1.6)	2/69 (2.9)
Level 2 (>2X ULN)	1/67 (1.5)	1/64 (1.6)	1/69 (1.4)
Level 3 (>3X ULN)	0/67	1/64 (1.6)	0/69
Prothrombin time, high (sec)			
Level 1 (>1.1XULN)	4/62 (6.5)	3/57 (5.3)	1/61 (1.6)
Level 2 (>1.3XULN)	1/62 (1.6)	1/57 (1.8)	1/61 (1.6)
Level 3 (>1.5XULN)	1/62 (1.6)	1/57 (1.8)	1/61 (1.6)

Source: ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data;

ULN, upper limit of normal

7.6.2.8. Vital-Sign Analyses, Study MG0003

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.

[Table 56](#) shows shifts in vital signs data from baseline visit during the double-blind placebo-controlled treatment period in Study MG0003. Normal to high shifts from baseline with frequency of at least 5% higher in the rozanolixizumab arm compared to placebo occurred in respiratory rate (11.3% versus 4.8%) and in diastolic blood pressure (rozanolixizumab ≈10 mg/kg dose arm only; 26.1% versus 20.9%). There were no shifts greater than 5% in systolic blood pressure, pulse rate, temperature, and bodyweight in the rozanolixizumab arm compared to placebo.

[Table 57](#) shows proportion of subjects with vital signs data meeting specific criteria specified in Appendix B of the preBLA meeting minutes dated July 19, 2022. The proportion of subjects with respiratory rate >20 breaths per minute and those with diastolic blood pressure >90 mm Hg was higher in the rozanolixizumab group compared to placebo (18% versus 11.9% and 30.8% versus 25.8%, respectively). No subjects receiving rozanolixizumab experienced increase in Fridericia corrected QT interval duration.

Table 56. Vital Sign Data Shifts From Baseline to Post Baseline, Safety Population, Study MG0003

Parameter	Shift From Baseline Category	Placebo N=67 n/N _w (%)	RLZ ≈7 mg/kg N=64 n/N _w (%)	RLZ ≈10 mg/kg N=69 n/N _w (%)	RLZ Total N=133 n/N _w (%)
Respiratory rate (breaths/min)	Normal to High	3/62 (4.8)	8/59 (13.6)	6/65 (9.2)	14/124 (11.3)
	Normal to Low	0/62 (0)	0/59 (0)	0/65 (0)	0/124 (0)
Temperature (°C)	Normal to High	0/67 (0)	1/64 (1.6)	1/69 (1.4)	2/133 (1.5)
	Normal to Low	16/67 (23.9)	13/64 (20.3)	12/69 (17.4)	25/133 (18.8)
Pulse rate (bpm)	Normal to High	1/67 (1.5)	2/64 (3.1)	3/69 (4.3)	5/133 (3.8)
	Normal to Low	10/67 (14.9)	8/64 (12.5)	4/69 (5.8)	12/133 (9)
Body weight (kg)	Normal to High	0/67 (0)	0/64 (0)	0/69 (0)	0/133 (0)
	Normal to Low	0/67 (0)	0/64 (0)	0/69 (0)	0/133 (0)
QTcF (ms)	Normal to High	1/67 (1.5)	0/64 (0)	0/69 (0)	0/133 (0)
	Normal to Low	0/67 (0)	0/64 (0)	2/69 (2.9)	2/133 (1.5)
Systolic blood pressure (mmHg)	Normal to High	16/67 (23.9)	9/64 (14.1)	14/69 (20.3)	23/133 (17.3)
	Normal to Low	1/67 (1.5)	1/64 (1.6)	0/69 (0)	1/133 (0.8)
Diastolic blood pressure (mmHg)	Normal to High	14/67 (20.9)	10/64 (15.6)	18/69 (26.1)	28/133 (21.1)
	Normal to Low	1/67 (1.5)	0/64 (0)	1/69 (1.4)	1/133 (0.8)

Source: advs.xpt, adeg.xpt; Software: R

Duration is from day 1 to day 43 (Treatment period).

Normal ranges for parameters are as follows: Respiratory rate, 12 to 20 breaths/min; Temperature, 36 to 38°C; Pulse Rate, 60 to 100bpm; Body weight, 7% decrease – 7% increase from baseline; QTcF, 350 to 450ms for Males, 360 to 460ms for Females; Systolic Blood Pressure, 90 to 140 mm Hg; Diastolic Blood Pressure, 50 to 90 mm Hg

Note: ANL01FL was not applied to this analysis.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with at least one analyte data; QTcF, Fridericia corrected QT interval; RLZ, rozanolixizumab; ≈, equivalent dose

Table 57. Vital Sign Data Meeting Specific Criteria Postbaseline, Safety Population, Study MG0003

Parameter	Placebo N=67 n/N _w (%)	RLZ≈7 mg/kg N=64 n/N _w (%)	RLZ≈10 mg/kg N=69 n/N _w (%)	RLZ Total N=133 n/N _w (%)
Respiratory rate (breaths/min)				
<12	1/67 (1.5)	0/64 (0)	0/69 (0)	0/133 (0)
>20	8/67 (11.9)	13/64 (20.3)	11/69 (15.9)	24/133 (18)
Pulse rate (bpm)				
<60	14/66 (21.2)	10/64 (15.6)	9/68 (13.2)	19/132 (14.4)
>100	2/66 (3)	3/64 (4.7)	3/68 (4.4)	6/132 (4.5)
Temperature (°C)				
<36	18/66 (27.3)	17/64 (26.6)	14/69 (20.3)	31/133 (23.3)
>38	0/66 (0)	1/64 (1.6)	1/69 (1.4)	2/133 (1.5)
Body weight				
≥7% Decrease from baseline	0/67 (0)	0/64 (0)	0/69 (0)	0/133 (0)
≥7% Increase from baseline	0/67 (0)	0/64 (0)	0/69 (0)	0/133 (0)
QTcF (ms)				
>450	5/66 (7.6)	0/64 (0)	0/69 (0)	0/133 (0)
>480	0/66 (0)	0/64 (0)	0/69 (0)	0/133 (0)
>500	0/66 (0)	0/64 (0)	0/69 (0)	0/133 (0)
Systolic blood pressure (mmHg)				
<90	1/67 (1.5)	1/64 (1.6)	0/69 (0)	1/133 (0.8)
>140	23/67 (34.3)	20/64 (31.2)	20/69 (29)	40/133 (30.1)
>160	3/67 (4.5)	2/64 (3.1)	2/69 (2.9)	4/133 (3.0)
Diastolic blood pressure (mmHg)				
<50	1/66 (1.5)	0/64 (0)	1/69 (1.4)	1/133 (0.8)
>90	17/66 (25.8)	20/64 (31.2)	21/69 (30.4)	41/133 (30.8)
>100	3/66 (4.5)	5/64 (7.8)	3/69 (4.3)	8/133 (6.0)

Source: advs.xpt, adeg.xpt; Software: R

Duration is day 1 to day 43 (Treatment period).

Note: ANL01FL was not applied to this analysis.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with at least one analyte data; QTcF, Fridericia corrected QT interval; RLZ, rozanolixizumab; ≈, equivalent dose

7.6.2.9. Subgroup Analyses, Study MG0003

[Table 58](#) summarizes the frequency of AEs by demographic groups in Study MG0003. Overall, there was no clinically significant difference in the frequency of AEs for the demographic parameters of age, sex, race, and baseline gMG status as defined by MGFA Class. However, the reviewer notes that there were a small number of subjects with the age greater than 65 years, the Asian and Black race, Hispanic ethnicity, the presence of anti-MuSK antibody and who were enrolled in the United States, and a conclusion regarding differences in the frequency of AEs in these subgroups cannot be drawn.

Table 58. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study MG0003

Characteristic	Placebo N=67 n/Ns (%)	RLZ≈7 mg/kg N=64 n/Ns (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI)	RLZ≈10 mg/kg N=69 n/Ns (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI)	RLZ Total N=133 n/Ns (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI)
Sex, n (%)							
Female	33/47 (70.2)	32/38 (84.2)	14.0 (-3.5, 31.5)	30/36 (83.3)	13.1 (-4.7, 31.0)	62/74 (83.8)	13.6 (-2.0, 29.1)
Male	12/20 (60.0)	20/26 (76.9)	16.9 (-10.0, 43.8)	27/33 (81.8)	21.8 (-3.4, 47.0)	47/59 (79.7)	19.7 (-4.1, 43.5)
Age group, years, n (%)							
≤18 yrs	1/1 (100)	0/0 (NA)	NA	0/0 (NA)	NA	0/0 (NA)	NA
≥65 yrs	14/16 (87.5)	11/16 (68.8)	-18.8 (-46.7, 9.2)	13/17 (76.5)	-11.0 (-36.9, 14.8)	24/33 (72.7)	-14.8 (-37.0, 7.4)
19 to <65 yrs	30/50 (60.0)	41/48 (85.4)	25.4 (8.6, 42.3)	44/52 (84.6)	24.6 (7.9, 41.4)	85/100 (85.0)	25.0 (9.7, 40.3)
Age group 2, years, n (%)							
≥75 yrs	7/7 (100)	3/4 (75.0)	-25.0 (-67.4, 17.4)	4/5 (80.0)	-20.0 (-55.1, 15.1)	7/9 (77.8)	-22.2 (-49.4, 4.9)
Race, n (%)							
Asian	2/5 (40.0)	8/9 (88.9)	48.9 (1.3, 96.5)	6/7 (85.7)	45.7 (-4.4, 95.9)	14/16 (87.5)	47.5 (1.6, 93.4)
Black or African American	0/1 (0)	0/0 (NA)	NA	3/4 (75.0)	75.0 (32.6, 117.4)	3/4 (75.0)	75.0 (32.6, 117.4)
Native Hawaiian or other Pacific Islander	0/1 (0)	0/0 (NA)	NA	0/0 (NA)	NA	0/0 (NA)	NA
White	32/46 (69.6)	31/39 (79.5)	9.9 (-8.4, 28.3)	41/51 (80.4)	10.8 (-6.4, 28.0)	72/90 (80.0)	10.4 (-5.2, 26.1)
Missing	11/14 (78.6)	13/16 (81.2)	2.7 (-26.1, 31.4)	7/7 (100)	21.4 (-0.1, 42.9)	20/23 (87.0)	8.4 (-17.1, 33.9)
Ethnicity, n (%)							
Hispanic or Latino	3/5 (60.0)	4/5 (80.0)	20.0 (-35.4, 75.4)	2/3 (66.7)	6.7 (-61.8, 75.1)	6/8 (75.0)	15.0 (-37.4, 67.4)
Not Hispanic or Latino	31/48 (64.6)	37/45 (82.2)	17.6 (0.1, 35.2)	49/60 (81.7)	17.1 (0.4, 33.8)	86/105 (81.9)	17.3 (1.9, 32.7)
Missing	11/14 (78.6)	11/14 (78.6)	0 (-30.4, 30.4)	6/6 (100)	21.4 (-0.1, 42.9)	17/20 (85.0)	6.4 (-20.2, 33.0)
Is in United States, n (%)							
United States	12/16 (75.0)	9/10 (90.0)	15.0 (-13.2, 43.2)	12/15 (80.0)	5.0 (-24.3, 34.3)	21/25 (84.0)	9.0 (-16.6, 34.6)
Non-United States	33/51 (64.7)	43/54 (79.6)	14.9 (-2.0, 31.9)	45/54 (83.3)	18.6 (2.2, 35.1)	88/108 (81.5)	16.8 (1.8, 31.8)
MGFA disease class at baseline, n (%)							
Class Iia	7/11 (63.6)	11/12 (91.7)	28.0 (-4.4, 60.5)	11/14 (78.6)	14.9 (-20.7, 50.6)	22/26 (84.6)	21.0 (-10.7, 52.6)
Class Iib	7/12 (58.3)	11/16 (68.8)	10.4 (-25.6, 46.4)	11/13 (84.6)	26.3 (-7.8, 60.4)	22/29 (75.9)	17.5 (-14.4, 49.5)
Class IIIa	22/28 (78.6)	17/20 (85.0)	6.4 (-15.4, 28.2)	22/27 (81.5)	2.9 (-18.2, 24.0)	39/47 (83.0)	4.4 (-14.2, 23.0)
Class IIIb	7/13 (53.8)	10/13 (76.9)	23.1 (-12.4, 58.6)	11/13 (84.6)	30.8 (-2.7, 64.2)	21/26 (80.8)	26.9 (-4.1, 58.0)
Class Iva	1/2 (50.0)	3/3 (100)	50.0 (-19.3, 119.3)	2/2 (100)	50.0 (-19.3, 119.3)	5/5 (100)	50.0 (-19.3, 119.3)
Class Ivb	1/1 (100)	0/0 (NA)	NA	0/0 (NA)	NA	0/0 (NA)	NA

Characteristic	Placebo N=67 n/N_s (%)	RLZ≈7 mg/kg N=64 n/N_s (%)	RLZ≈7 mg/kg vs. Placebo Risk Difference (%) (95% CI)	RLZ≈10 mg/kg N=69 n/N_s (%)	RLZ≈10 mg/kg vs. Placebo Risk Difference (%) (95% CI)	RLZ Total N=133 n/N_s (%)	RLZ Total vs. Placebo Risk Difference (%) (95% CI)
Thymectomy, n (%)							
No	25/36 (69.4)	25/32 (78.1)	8.7 (-12.1, 29.5)	40/49 (81.6)	12.2 (-6.4, 30.7)	65/81 (80.2)	10.8 (-6.6, 28.2)
Yes	20/31 (64.5)	27/32 (84.4)	19.9 (-1.2, 40.9)	17/20 (85.0)	20.5 (-2.5, 43.5)	44/52 (84.6)	20.1 (0.6, 39.6)
Myasthenia crisis in the past, n (%)							
No	27/44 (61.4)	37/44 (84.1)	22.7 (4.7, 40.7)	41/51 (80.4)	19.0 (1.0, 37.1)	78/95 (82.1)	20.7 (4.4, 37.1)
Yes	18/23 (78.3)	15/19 (78.9)	0.7 (-24.2, 25.6)	15/17 (88.2)	10.0 (-12.8, 32.7)	30/36 (83.3)	5.1 (-15.7, 25.9)
Missing	0/0 (NA)	0/1 (0)	NA	1/1 (100)	NA	1/2 (50.0)	NA
Baseline AChR status, n (%)							
Negative	7/11 (63.6)	5/5 (100)	36.4 (7.9, 64.8)	5/7 (71.4)	7.8 (-36.1, 51.7)	10/12 (83.3)	19.7 (-15.7, 55.1)
Positive	35/53 (66.0)	44/54 (81.5)	15.4 (-1.0, 31.9)	49/58 (84.5)	18.4 (2.7, 34.2)	93/112 (83.0)	17.0 (2.5, 31.5)
Unknown	3/3 (100)	3/5 (60.0)	-40.0 (-82.9, 2.9)	3/4 (75.0)	-25.0 (-67.4, 17.4)	6/9 (66.7)	-33.3 (-64.1, -2.5)
Baseline MuSK status, n (%)							
Negative	39/57 (68.4)	45/55 (81.8)	13.4 (-2.4, 29.2)	51/61 (83.6)	15.2 (-0.0, 30.4)	96/116 (82.8)	14.3 (0.4, 28.2)
Positive	4/8 (50.0)	4/4 (100)	50.0 (15.4, 84.6)	3/4 (75.0)	25.0 (-29.8, 79.8)	7/8 (87.5)	37.5 (-4.0, 79.0)
Unknown	2/2 (100)	3/5 (60.0)	-40.0 (-82.9, 2.9)	3/4 (75.0)	-25.0 (-67.4, 17.4)	6/9 (66.7)	-33.3 (-64.1, -2.5)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between rozanolixizumab and placebo

Abbreviations: AChR, Acetylcholine receptor; CI, confidence interval; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle specific tyrosine kinase; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; RLZ, rozanolixizumab

7.6.2.10. Exposure-Adjusted Analyses, Study MG0003

Not applicable.

7.7. Key Safety Review Issues

7.7.1. Infections

Issue

TEAEs related to infections were among the most frequently reported adverse events in Study MG0003.

Background

The topic of infections was of special interest. The Applicant's proposed label notes that infections were among the most frequently reported AEs in clinical studies and includes infections in Warnings and Precautions.

Given the mechanism of drug action, treatment with rozanolixizumab results in a reduction of circulating immunoglobulin G (IgG) and reduced IgG levels are associated with an increased risk of infections ([Furst 2009](#)). Bacterial infections of the respiratory tract are the most common types of infection seen in individuals with reduced IgG levels. Based on the available literature review, it is unclear at what IgG level the risk for infections becomes apparent. The overall risk may also depend on the age, concomitant medication, and underlying disease in individual patients. Specifically, MG patients have a high susceptibility for respiratory tract infections and sepsis due to bulbar and respiratory muscle weakness, and concomitant immunomodulating therapies administered as standard MG care ([Prior et al. 2018](#); [Sipila et al. 2019](#); [Kassardjian et al. 2020](#)).

Assessment

Subjects with serum total IgG levels ≤ 5.5 g/L were not enrolled in Study MG0003. Treatment with rozanolixizumab resulted in the reduction in total serum IgG levels compared to placebo. As early as the first follow-up visit on day 8, one week after the first infusion, median total IgG levels were decreased by 44.8% and 52.8% in rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg arms. The median maximum decrease from baseline was -73.2% (range, -95.5% to 5.7%) in rozanolixizumab ≈ 7 mg/kg treatment group and -78.9% (range, -92.2% to -46.5%) in rozanolixizumab ≈ 10 mg/kg treatment group compared to -9.0% (range, -49% to 4.8%) in the placebo group (source: CSR MG0003, Table 9-2). The lowest serum IgG levels were 0.3 g/L in rozanolixizumab ≈ 7 mg/kg treatment group and 0.46 g/L in rozanolixizumab ≈ 10 mg/kg treatment group observed at day 29 compared to placebo 6.17 g/L on the same day. By day 99, the median IgG levels had increased to 13% and 9% of the baseline value in rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg treatment groups, respectively.

[Table 59](#) shows in Study MG0003, the TEAEs of infections occurred at higher frequency in rozanolixizumab ≈ 10 mg/kg arm (n=21; 30.4%) compared to the rozanolixizumab ≈ 7 mg/kg arm (n=10; 15.6%) and placebo arm (n=13; 19.4%). The most common infections were upper

respiratory tract infections and herpes simplex. One subject in rozanolixizumab ≈ 10 mg/kg arm developed an opportunistic infection caused by herpes zoster virus. None of the subjects treated with rozanolixizumab had serious infections. There were no deaths in Study MG0003. In one subject rozanolixizumab ≈ 10 mg/kg treatment was discontinued due to TEAEs of metastatic squamous cell carcinoma and deep venous thrombosis and the subject had oral herpes. About two thirds of the events were considered mild intensity and no subject had severe infection while on rozanolixizumab treatment.

Table 59. TEAEs Belonging to the SOC of Infections and Infestations With Higher Frequency in Rozanolixizumab ≈ 7 mg/kg or ≈ 10 mg/kg Than Placebo, Safety Population, Study MG0003

Preferred Term	Rozanolixizumab ≈ 7 mg/kg (N=64) n (%)	Rozanolixizumab ≈ 10 mg/kg (N=69) n (%)	Placebo (N=67) n (%)
Any infection or infestation	10 (15.6)	21 (30.4)	13 (19.4)
Upper respiratory tract infection	2 (3.1)	1 (1.4)	1 (1.5)
Rhinitis	0	1 (1.4)	0
Sinusitis	0	1 (1.4)	0
Nasopharyngitis	1 (1.6)	5 (7.2)	3 (4.5)
Pneumonia	0	1 (1.4)	0
Respiratory tract infection viral	1 (1.6)	1 (1.4)	0
Herpes simplex	0	1 (1.4)	0
Oral herpes	0	3 (4.3)	0
Gastroenteritis viral	1 (1.6)	0	0
Skin infection	1 (1.6)	0	0
Cellulitis	0	1 (1.4)	0
Conjunctivitis	0	1 (1.4)	0
Herpes zoster	0	1 (1.4)	0
Sepsis	0	1 (1.4)	0
Cystitis	0	1 (1.4)	0
Urinary tract infection bacterial	0	1 (1.4)	0
Tooth abscess	1 (1.6)	1 (1.4)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs.

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

In Safety Pool S1 pooled from Studies MG0003, MG0004, and MG0007, out of 196 subjects treated with rozanolixizumab, 94 (48%) subjects reported TEAEs of infections (see Section [17.6](#) [Table 102](#) and [Table 103](#)). The frequency of infections was relatively higher in rozanolixizumab ≈ 10 mg/kg dose arm (55.4%) compared to ≈ 7 mg/kg dose arm (40%), which is similar to that observed in the double-blind treatment cycle in Study MG0003. The most common infections were upper respiratory tract infections (17.3%), COVID-19 (14.3%), urinary tract infections (8.7%), and herpes simplex (5.6%). There were no opportunistic infections. Serious infections occurred in 8 (4.1%) subjects including COVID-19 (n=4), multilobar pneumonia due to unidentified pathogen (n=1), E. coli urosepsis (n=1), appendicitis complicated with liver abscess, peritonitis, and cholecystitis (n=1), and aseptic meningitis (n=1). The SAE of aseptic meningitis led to treatment discontinuation in one subject (see case narrative below). TEAEs of infections that led to treatment discontinuation in 6 (3.1%) subjects included oral herpes, complicated

appendicitis, COVID-19, COVID-19 pneumonia, pneumonia, and urosepsis in one subject each (see Section 17.5 [Table 101](#)). In the open-label extension Study MG0007, one subject died in the setting of multilobar pneumonia in which no pathogen was identified and a role of rozanolixizumab cannot be ruled out. Two deaths were attributed to COVID-19 pneumonia in unvaccinated individuals. The TEAE of positive Interferon gamma release (IGRA) test led to treatment discontinuation in two subjects in Study MG0007. Case narratives for these subjects do not provide a clinical follow up regarding whether they were diagnosed with latent or active tuberculosis disease. Both subjects were IGRA positive upon entry to Study MG0007 (see Section [17.5](#)). The Applicant has reported that none of the subjects were diagnosed with active tuberculosis or hepatitis in the phase 3 clinical studies of rozanolixizumab.

In 120-day safety update (cutoff date October 7, 2022), two subjects discontinued rozanolixizumab ≈ 10 mg/kg dose treatment due to TEAEs of appendicitis (SAE, n=1) and endocarditis (n=1). The description of endocarditis leading to death was included in the original BLA submission. No new cases of aseptic meningitis were identified. Compared to the original BLA submission, there were no clinically significant changes in the relative incidence of common TEAEs ($\geq 5\%$ frequency) in the safety update. There were two new TEAEs of decreased blood immunoglobulin which is expected given the mechanism of drug action; one event led to temporary drug discontinuation.

Aseptic Meningitis

At the time of this review, there have been three SAEs of aseptic meningitis reported as drug-induced aseptic meningitis across the rozanolixizumab development program including, one event in one subject receiving rozanolixizumab ≈ 10 mg/kg dose treatment during the ongoing open-label MG0007 study and one event each in two subjects randomized to blinded rozanolixizumab or placebo treatment in the study evaluating rozanolixizumab for another indication. In the BLA submission, the Applicant provided case narratives of all three subjects (see Module 2.7.4. Section 2.1.7.2.2. Page 97 dated September 29, 2022, [III.17](#)).

For the rozanolixizumab gMG program, the SAE of aseptic meningitis occurred in one subject out of total 196 subjects (0.005%) in the Safety Pool S1.

In response to an IR dated (b) (4), the Applicant indicated that these three cases are the only known cases of aseptic meningitis in their rozanolixizumab development program (n=555; 0.005%). All three subjects experienced headache, nuchal rigidity, and fever within 2 days after the first infusion of rozanolixizumab ≈ 10 mg/kg dose (n=1) in the MG0007 study or blinded treatment (n=2) in the study for other indication. Cerebrospinal fluid (CSF) was notable for pleocytosis and normal protein in the gMG subject and pleocytosis with elevated protein in the subjects with the other indication. Symptoms improved after two days. All subjects recovered without sequelae as outlined in the brief case summaries below as provided by the Applicant:

BLA761286:

- Subject MG0007-(b) (6): 51-year-old female with gMG who experienced severe headache, nuchal rigidity, fever, diarrhea, nausea, and vomiting 1.5 days after the first infusion of rozanolixizumab 10 mg/kg infusion in Study MG0007. Concomitant medications included prednisolone, pyridostigmine, and azathioprine. The subject was hospitalized, and

CSF was notable for a monocytic pleocytosis of 509 cells/ μ L and normal protein. CSF infectious studies were negative, including viral polymerase chain reactions (PCRs), fungal cultures, and bacterial cultures (see [17.4](#)). Magnetic resonance imaging (MRI) demonstrated frontal periventricular meningeal enhancement. The subject was treated with ceftriaxone, acyclovir, and dexamethasone, which were stopped after her headache improved (after two days). The subject recovered in 5 days and was discharged. The subject underwent repeat lumbar puncture at 27 days post-event onset, and the pleocytosis resolved (see also [17.4](#)). The study drug was withdrawn due to aseptic meningitis and the subject discontinued from the study. The SAE was considered severe and related to rozanolixizumab by the reviewer.

IND (b) (4), rozanolixizumab for the treatment of myelin oligodendrocyte glycoprotein antibody disease (MOG-AD)

- Subject MOG0001-(b) (6): 27-year-old male who experienced moderate headache, fever, and neck stiffness 2 days after the first infusion of study treatment rozanolixizumab 560 mg or placebo (blinded) in the study. Concomitant medications included prednisolone and trimethoprim/sulfamethoxazole (for 9 months). CSF was notable for lymphocytic pleocytosis (170/uL), elevated protein (75 mg/dL), and normal glucose. CSF cultures were negative, and viral PCRs were not performed. MRI showed findings consistent with the underlying disease and an incidental arachnoid cyst. The headache improved 2 days after onset, and he was treated with loxoprofen. The subject was considered recovered after 54 days. The SAE was considered related to rozanolixizumab by the reviewer. Hospitalization was recommended however, subject requested not to be hospitalized and was withdrawn from the study.
- Subject MOG0001-(b) (6): 33-year-old male who experienced mild headache and fever 2 days after the first infusion of study treatment rozanolixizumab 560 mg or placebo (blinded) in the study. Concomitant medications included tacrolimus (discontinued one month prior to study enrollment), prednisolone, trimethoprim/sulfamethoxazole (since 2018), and fexofenadine (since 2020). CSF was notable for pleocytosis (equally neutrophilic and monocytic), elevated protein (89 mg/DL), slightly elevated glucose (78 mg/dL), and negative bacterial cultures. Viral PCR testing was not performed. MRI showed findings consistent with the underlying disease. The subject was treated with dexamethasone, meropenem, vancomycin, acyclovir, and paracetamol. The headache and fever improved after 2 days, and the event was considered resolved at 6 days. The SAE was considered related to rozanolixizumab by the reviewer. The subject was hospitalized and was withdrawn from the study.

In Study MG0003, out of 133 subjects treated with rozanolixizumab, 58 (43.6%) subjects who experienced headaches had associated symptoms of fevers (29.3%), nausea (20.7%), vomiting (3.4%), and neck pain (3.4%). In the Safety Pool S1 from the Studies MG0003, MG0004, and MG0007 out of 196 subjects treated with rozanolixizumab, 98 (50%) subjects experienced headaches and had associated symptoms of fever (30.6%), nausea (28.6%), vomiting (10.2%) and neck pain (6.1%). None of these subjects underwent a lumbar puncture during the study. (source: adae.xpt; Software: R).

The Applicant indicated in their information request (IR) response dated (b) (4) that none of the 25 subjects who developed a serious or severe headache across the rozanolixizumab development program underwent lumbar puncture. Of these 25 subjects, three subjects were healthy volunteers and received a single dose. Of the other 22 subjects who developed a serious or severe headache in the setting of repeated treatment, 18 continued the treatment and rechallenge was positive in two subjects, one of whom discontinued the treatment. These subjects had associated symptoms of fever (40%), neck pain (32%), nausea and vomiting (52%). In the updated investigator's brochure dated September 1, 2022, the Applicant concluded that the available information supported a potential causal relationship between rozanolixizumab and the TEAE of aseptic meningitis.

[Table 60](#) shows that the frequency of infections in the subjects with abnormal laboratory values of serum IgG levels and blood cell counts was not higher than that reported in the overall population treated with rozanolixizumab in Study MG0003. However, in pooled phase 3 Studies MG0003, MG0004, and MG0007 (Safety Pool S1), compared to all subjects, a higher frequency of infections was reported in subjects with low lymphocyte counts (57% versus 48%) (Table 61). The reviewer cannot conclude a role of low neutrophil and leukocyte counts in the TEAEs of infections in the subjects treated with rozanolixizumab because the number of subjects is relatively small (fewer than 20) in the phase 3 studies.

Table 60. Frequency of TEAEs in SOC Infections and Infestations by Low IgG levels, and Low Leukocyte, Lymphocyte, and Neutrophil Count Status at any Point of Time, Safety Population, Study MG0003

Population	Number of Subjects Treated With RLZ	Number of Infection Events in Subjects Treated With RLZ	Number of Infection Events/Number of Subjects Treated With RLZ (%)	Number of Subjects Treated With Placebo	Number of Infection Events in Subjects Treated With Placebo	Number of Infection Events/Number of Subjects Treated With Placebo (%)
All subjects	133	31	23.3	67	13	19.4
Serum IgG <2.0 g/L	57	12	21.1	0	0	0
Serum IgG ≤1.0 g/L	11	2	18.2	0	0	0
Low leukocytes ¹	13	1	10.0	8	1	12.5
Low lymphocytes ²	45	9	22.0	28	6	21.4
Low neutrophils ³	19	4	23.5	10	2	20.0

Source: adae.xpt, adlb.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose.

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

¹less than 3500 cells per microliter

²less than 1000 cells per microliter

³less than 2000 cells per microliter

Abbreviations: IgG, immunoglobulin G; RLZ, rozanolixizumab; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 61. Frequency of TEAEs in SOC Infections and Infestations by Low IgG levels, and Low Leukocyte, Lymphocyte, and Neutrophil Count Status at Any Point of Time, Safety Pool S1, Studies MG0003, MG0004, MG0007

Population	Number of Subjects Treated With RLZ	Number of Infection Events in Subjects Treated With RLZ	Number of Infection Events/Number of Subjects Treated With RLZ (%)
All subjects	196	94	48.0
Serum IgG <2.0 g/L	100	48	48.0
Serum IgG ≤1.0 g/L	29	11	37.9
Low leukocytes ¹	29	14	48.3
Low lymphocytes ²	86	49	57.0
Low neutrophils ³	36	16	44.4

Source: iss adae.xpt, adsl.xpt (pool S1), combined individual studies ad b.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as:

MG0003 – as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs;

MG0004 – as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab;

MG0007 – defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration:

MG0003 – 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks;

MG0004 – first 6 weeks of all study subjects;

MG0007 – is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

¹less than 3500 cells per microliter

²less than 1000 cells per microliter

³less than 2000 cells per microliter

Abbreviations: IgG, immunoglobulin G; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event

Conclusion

The reviewer notes that rozanolixizumab may increase the risk of infection. In Study MG0003, TEAEs of infections were among the most frequently reported adverse events (>10%) in subjects treated with rozanolixizumab. The most common infections were upper respiratory tract infection and herpes simplex. Similar TEAEs of infections were observed in the open-label extension Studies MG0004 and MG0007. The frequency of infections appeared higher in the rozanolixizumab ≈ 10 mg/kg group compared to rozanolixizumab ≈ 7 mg/kg group. In these open-label studies, there were reports of SAEs (4.1%), TEAEs leading to treatment discontinuation (3.6%) and fatal TEAEs (1.5%; n=3) belonging to the SOC of Infections and Infestations.

An SAE of aseptic meningitis has been reported in one subject with gMG and two subjects with MOG-AD which led to hospitalization and discontinuation of rozanolixizumab in clinical studies. Moreover, in clinical studies, subjects treated with rozanolixizumab experienced headaches associated with fever, nausea, vomiting, and neck pain. These findings suggest that rozanolixizumab has the potential to cause aseptic meningitis.

Given the mechanism of action, treatment with rozanolixizumab led to reduction in the serum IgG levels. The sample size is not adequately powered to conclusively determine whether these reduced IgG levels contributed to infections in patients treated with rozanolixizumab. In pooled phase 3 studies, the frequency of infections was higher in the subjects with low lymphocyte counts. The reviewer could not determine a causative link between abnormal neutrophil and leukocyte counts and the risk of infection in subjects treated with rozanolixizumab due to small sample size (less than 20 subjects).

It is unknown based on phase 3 clinical studies whether treatment with rozanolixizumab increases the risk of reactivation of hepatitis or tuberculosis in gMG patients. The Applicant reported that there were no cases of active tuberculosis in their phase 3 studies of rozanolixizumab in patients with gMG. The studies did not enroll hepatitis carriers. There were two cases of positive IGRA test on entry to an open-label study. This test does not differentiate latent tuberculosis from active tuberculosis disease. The reviewer recommends increased pharmacovigilance for reactivation of hepatitis or TB in subjects treated with rozanolixizumab.

The reviewer recommends a Warning and Precaution Statement for infections in labeling for rozanolixizumab based on the class of drug, pharmacology, known mechanism of action by inhibition of FcRn receptor, and the observed frequency and seriousness of TEAEs belonging to system organ class (SOC) Infections and Infestations in the phase 3 clinical studies. The reviewer notes that infections are included in the Warning and Precautions section of the label for efgartigimod, a previously approved FcRn inhibitor drug for the treatment of patients with gMG who are anti-AChR antibody positive.

Because there were three cases of SAEs of aseptic meningitis which led to hospitalization and discontinuation of rozanolixizumab in clinical studies, the reviewer recommends a Warning and Precaution Statement for aseptic meningitis in labeling for rozanolixizumab.

There is also a concern regarding potential for more serious outcomes in the postmarketing period where subjects are monitored less frequently than in a clinical study setting, therefore a Warnings and Precautions statement may mitigate potentially serious outcomes of infections by alerting providers to the risk.

7.7.2. Headaches

Issue

TEAEs related to headaches were the most frequently reported adverse events in Study MG0003.

Background

The topic of headaches was of special interest as the Applicant's proposed label notes that headaches were the most frequently reported aEs in clinical studies. The underlying mechanism for the most common TEAE of headache is unknown.

Assessment

In Study MG0003, a total of 58 (43.6%) subjects out of 133 subjects treated with rozanolixizumab experienced headaches compared to 13 (19.4%) subjects out of 67 subjects in the placebo arm (Table 62). Most headaches were reported after the first infusion and did not increase with repeat treatments. In a majority of the subjects, the headaches were mild to moderate intensity and resolved without sequelae. A total of 7 (5.3%) subjects treated with rozanolixizumab experienced severe headache (see case narratives below). Of these seven subjects, six subjects were treated with the rozanolixizumab $\approx$ 10 mg/kg dose and one subject was treated with the rozanolixizumab $\approx$ 7 mg/kg dose. One subject (MG0003/ (b) (6)) in rozanolixizumab $\approx$ 7 mg/kg arm discontinued treatment due to severe headache associated with fevers, photophobia, phonophobia, nausea, and vertigo (see Section 7.6.2.4). One subject (MG0003/ (b) (6)) in rozanolixizumab $\approx$ 10 mg/kg arm was hospitalized due to severe headache (see Section 7.6.2.3). Severe or serious TEAEs of headaches were not observed in the placebo arm.

Table 62. TEAEs of Headache (HLGT) by Maximum Intensity, Safety Population, Study MG0003

Preferred Term	Placebo N=67	Rozanolixizumab $\approx$ 7 mg/kg N=64	Rozanolixizumab $\approx$ 10 mg/kg N=69
Intensity	n (%)	n (%)	n (%)
Headache, any intensity	13 (19.4)	29 (45.3)	26 (37.7)
Mild	10 (14.9)	17 (26.6)	9 (13.0)
Moderate	3 (4.5)	11 (17.2)	11 (15.9)
Severe	0	1 (1.6)	6 (8.7)
Migraine, any intensity	0	2 (3.1)	2 (2.9)
Mild	0	1 (1.6)	1 (1.4)
Moderate	0	1 (1.6)	1 (1.4)
Severe	0	0	0

Source: MG0003 CSR Table 9.3.4.1

Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Coded as MedDRA preferred terms.

For subjects with multiple events, the event is counted only once within the category.

Abbreviations: HLGT, high level group term; N, number of patients in treatment arm; n, number of patients with adverse event; TEAE, treatment-emergent adverse event

Case Narratives for TEAEs of Severe Headache, Study MG0003 (Source: Module 5.3.5.1. MG0003 Narratives)

- Subject MG0003/ (b) (6): 53-year-old female experienced a nonserious TEAE of pulsatile holocephalic severe headache 4 days after the first SC infusion of rozanolixizumab ≈ 7 mg/kg dose. The headache progressed from moderate to severe intensity over 2 days. The subjects reported fevers, nausea, photophobia, phonophobia, and vertigo. The subject was treated with ibuprofen and paracetamol. Rozanolixizumab treatment was withdrawn due to headache. The event was resolved 4 days after onset. The subject had a history of severe headache with nausea in the preceding five years before enrolling into the study. Given the timing of onset, it is likely drug-related. An infectious etiology cannot be excluded.
- Subject MG0003/ (b) (6): 26-year-old female experienced a serious TEAE of severe headache, 10 days after the first and third day after the second SC infusion of rozanolixizumab ≈ 10 mg/kg dose. The subject woke up with a moderately severe throbbing and pressurized headache which gradually worsened during the day making her bedridden. The subject had exacerbation of headache with light, sound, and movement. The subject reported nausea but no vomiting, neck stiffness, or fever. Treatment with paracetamol had no effect on headache. The subject was admitted to an emergency room for less than 12 hours. The subject had a good response with ibuprofen and metaclopramide. The event was considered resolved 2 days after onset. The dosing regimen for rozanolixizumab was unchanged and the subject completed all six planned doses in the double-blind treatment cycle and later enrolled into the OLE Study MG0007. The subject again experienced a milder headache after second dose but that was attributed by the subject to the use of contact lenses. This AE is likely related to rozanolixizumab given the timing of the onset and a positive rechallenge.
- Subject MG0003/ (b) (6): 42-year-old female experienced a nonserious TEAE of non-throbbing bilateral severe headache 3 days after the first SC infusion of rozanolixizumab ≈ 10 mg/kg dose. The headache reached maximum intensity 10 on visual analog scale with vomiting and responded minimally to paracetamol during the first 24 hours from symptom onset. The event was considered resolved 3 days after onset. The dosing regimen for rozanolixizumab was unchanged due to headache. Later, she discontinued rozanolixizumab due to TEAE of pruritis 29 days after the first and eighth day after the fourth infusion. There were no reports of positive rechallenge with the subsequent three doses. The TEAE of headache was considered severe and related to rozanolixizumab given the suggestive time of onset.
- Subject MG0003/ (b) (6): 30-year-old male experienced nonserious TEAEs of severe headache and fevers (38.5°C) 3 days after the first SC infusion of rozanolixizumab ≈ 10 mg/kg dose. The following day the intensity of headache decreased, and fevers resolved. The event was considered resolved 1 day after onset. The dosing regimen for rozanolixizumab was unchanged and the subject completed all 6 planned doses in the double-blind treatment cycle and later enrolled into the OLE Study MG0007. There were no reports of positive rechallenge with the subsequent doses. A lumbar puncture was not done. SARS-CoV-2 test was negative normal. Other viral origins for headache and fever cannot be

excluded. Given the time of onset, the aEs of headaches and fevers were likely related to rozanolixizumab.

- Subject MG0003/ (b) (6): 58-year-old female experienced a nonserious TEAE of severe migraine-like headache, 18 days after the first and third day after the third SC infusion of rozanolixizumab ≈ 10 mg/kg dose. Past medical history was notable for migraine headaches. The headache was unilateral, throbbing/pulsating in nature, and worsened with activity. During the course of the headache, the subject also experienced nausea, infrequent vomiting, increased neck pain or stiffness, increased sensitivity to light and noise, increased sensitivity to smell, weakness on one side; and seeing shimmering lights, lines, dark spots, other shapes or colors before the eyes. Before the headache became severe, one-sided numbness of the lips, tongue, fingers, and legs that migrated was noted, which lasted less than an hour. No dizziness was noted. The subject received treatment with acetylsalicylic acid with caffeine and paracetamol. The event was considered resolved 2 days after onset. The dosing regimen for rozanolixizumab was unchanged due to the TEAE of headache. Later, the subject discontinued rozanolixizumab after the fourth infusion due to a serious TEAE of metastatic squamous cell carcinoma. There was no positive rechallenge with the subsequent doses. The AE of headache was likely related to rozanolixizumab given the time of onset.
- Subject MG0003/ (b) (6): 39-year-old male experienced a nonserious TEAE of severe headache 3 days after the first SC infusion of rozanolixizumab ≈ 10 mg/kg, which resolved 3 days after onset. The subject experienced a second nonserious TEAE of moderate headache 9 days after the first dose and 1 day after the second rozanolixizumab infusion. This second event resolved 3 days after onset. The subject completed a total of five infusions in the study. There was no positive rechallenge with the subsequent doses. The AE of headache was likely related to rozanolixizumab given the time of onset and a positive rechallenge.
- Subject MG0003/ (b) (6): 35-year-old female experienced a nonserious TEAE of severe headache 3 days after the first SC infusion of rozanolixizumab ≈ 10 mg/kg, which resolved 3 days after onset. The subject experienced a second nonserious TEAE of mild headache 9 days after the first dose and 1 day after the second rozanolixizumab infusion, which resolved on the same day. The subject experienced a third nonserious TEAE of mild headache 3 days after the fifth and final dose, which also resolved on the same day. The AE of headache was likely related to rozanolixizumab given the time of onset and a positive rechallenge.

In Safety Pool S1 pooled from Studies MG0003, MG0004, and MG0007, out of 196 subjects treated with rozanolixizumab, 98 (50%) subjects experienced headache including 52 (54.7%) subjects in the rozanolixizumab ≈ 7 mg/kg arm and 46 (45.5%) subjects in the rozanolixizumab ≈ 10 mg/kg arm. The incidence of headache did not increase with repeated treatment cycles. There were no serious TEAEs of headache in the open-label MG0004 and MG0007 studies. A total of 12 subjects experienced severe headache in Pool S1 including seven subjects in the double-blind Study MG0003 discussed above. In 120-day safety update, there were no additional cases of severe or serious headaches.

Case narrative for TEAEs of Severe Headache, Study MG0007 (Source: Module 5.3.5.2. MG0007 Narratives-120-day Safety Update Cutoff October 7, 2022):

- Subject MG0007- (b) (6): 56-year-old female experienced a nonserious TEAE of a mild headache 1 day after the first SC infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0003, which resolved on the same day. The subject experienced another TEAE of a mild headache 1 day after fourth and then a moderate headache after fifth infusion, both of which resolved within 1 day after onset. The subject completed six planned doses in Study MG0003. Subsequently, the subject received about 6 months of weekly SC infusions of rozanolixizumab ≈ 7 mg/kg dose in the OLE Study MG0004 without any TEAEs. The subject discontinued MG0004 and enrolled into MG0007 study. The subject experienced a TEAE of mild headache during the seventh treatment cycle of rozanolixizumab ≈ 10 mg/kg. Later, the subject experienced a nonserious TEAE of severe headache 4 days after 26th infusion in Study MG0007, which resolved 3 days after onset. The subject continued the study treatment without any changes made to their rozanolixizumab dosing regimen. The AE of headache was likely related to rozanolixizumab given the time of onset and positive rechallenges.

Case Narratives for TEAEs of Severe Headache, Study MG0004 (Source: Module 5.3.5.2. MG0004 Narratives):

- Subject MG0004- (b) (6): 66-year-old female experienced a nonserious TEAE of moderate headache 2 days after the first SC infusion of rozanolixizumab ≈ 7 mg/kg in Study MG0003, which resolved within 1 day. The subject completed all six doses planned in the double-blind treatment cycle and enrolled into the OLE Study MG0004. The subject experienced a nonserious TEAE of bilateral pulsatile severe headache 2 days after receiving the first open-label dose of rozanolixizumab ≈ 10 mg/kg. The subject also experienced fevers (38.3°C), pelvic pain, dysuria with burning, and mild abdominal pain. The headache and fever improved the next day and the event was resolved in 2 days. A bacterial test confirmed urinary tract infection, which was treated with fosfomycin. The subject experienced another TEAE of mild headache after 24-week infusion and a nonserious TEAE of moderate headache after 51-week infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0004. The subject completed MG0004 study without any further events and enrolled into MG0007 study. The AE of headache was likely related to rozanolixizumab given the time of onset and positive rechallenges.
- Subject MG0004- (b) (6): 35-year-old female experienced a nonserious TEAE of severe headache 2 days after the first infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0004. The subject also experienced nausea, dizziness, neck pain or stiffness, increased sensitivity to light, and vomiting. The headache got worse with physical activity. The subject received metamizole, ibuprofen, and paracetamol as treatment for the headache. The event resolved 2 days after onset. The dosing regimen for rozanolixizumab was unchanged. The subject experienced mild headaches treated with paracetamol within 1 to 2 days of repeated weekly infusions of rozanolixizumab during the Study MG0004. The subject withdrew from the study after Week 14 dose. The subject had experienced two episodes of milder headaches after the first and sixth (final) infusion of placebo in Study MG0003. The subject had not experienced headache in the 5 years preceding the

study. The AE of headache was likely related to rozanolixizumab in Study MG0004 given the time of onset and positive rechallenges.

- Subject MG0004/ (b) (6): 60-year-old female experienced a nonserious TEAE of severe headache 3 days after the first infusion of rozanolixizumab $\approx$ 7 mg/kg dose. The subject described the headache as intermittent, pulsating feeling from the back of the head to the neck bilaterally associated with nausea, neck stiffness, phonophobia, photophobia, and tingling and numbness in the lower legs, weakness on “one side”, and pain on one side of head. The subject received diphenhydramine, paracetamol, and paracetamol-codeine combination for headache. The event resolved 7 days after onset. The subject transitioned into Study MG0007. The subject received placebo infusions in Study MG0003. The subject had no history of migraine or headache in the past. The subject was taking ramipril, amlodipine, and hydrochlorothiazide for hypertension. The TEAE of headache was likely related to rozanolixizumab given the time of onset.
- Subject MG0004/ (b) (6): 27-year-old female experienced a nonserious TEAE of severe headache 3 days after the first infusion of rozanolixizumab $\approx$ 7 mg/kg dose. The subject did not experience nausea, vomiting, or other neurological symptoms. The subject received ibuprofen, paracetamol, codeine, and paracetamol with tramadol for headache. The event resolved 3 days after onset. The subject received a total of five infusions in Study MG0004 and the drug was withdrawn due to pregnancy. The subject experienced MG crisis 39 days after the last infusion, which resolved with IVIg treatment. The subject had experienced two episodes of mild headache while receiving placebo infusions in Study MG0003. The AE of headache was likely related to rozanolixizumab given the time of onset.
- Subject MG0004/ (b) (6) (see MG0003/ (b) (6) for MG0003): 39-year-old male experienced a nonserious TEAE of severe headache 3 days after the first infusion of rozanolixizumab $\approx$ 7 mg/kg dose. The subject was treated with ibuprofen for the headache. The subject also experienced pyrexia which resolved on the same day. The subject experienced a repeat mild headache 3 days after week 6 infusion which resolved 3 days after onset. The subject received 23 infusions in Study MG0004 with no repeat episodes of headaches. The subject rolled into Study MG0007. The subject had experienced nonserious TEAEs of two episodes of moderate to severe headaches while receiving rozanolixizumab $\approx$ 10 mg/kg in Study MG0003. The AE of headache was likely related to rozanolixizumab given the time of onset.

Conclusion

Headache was the most commonly reported adverse events related to rozanolixizumab in the phase 3 studies reported by 50% of subjects (98 out of 196 subjects). In the placebo-controlled Study MG0003, headaches occurred at higher frequency in subjects treated with rozanolixizumab than placebo (43.6% versus 19.4%). Headaches were classified as migraine in 4 (3%) of subjects. There were no cases of tension headaches. The reviewer notes that the medical history of headache was balanced across the treatment groups at baseline. In phase 3 studies of subjects with gMG, there were 12 (6%) cases of severe headaches, one case of serious headache requiring hospitalization, and one case of headache that led to discontinuation of rozanolixizumab.

Headaches generally occurred within 1 to 4 days after the infusion and more commonly after the first infusion. Subjects with headaches also reported associated symptoms of nausea, dizziness, neck pain or stiffness, increased sensitivity to light, and vomiting. These subjects did not undergo evaluation for meningitis. The Applicant reported three subjects with aseptic meningitis in their rozanolixizumab studies, including one subject with gMG in Study MG0007 and two cases with myelin oligodendrocyte glycoprotein antibody disease (MOG-AD (see Section [II.7.7.1](#)). The pathogenesis of headache in the subjects treated with rozanolixizumab is unknown. Given the timeline of event in relation to rozanolixizumab infusion, it is possible that headaches represent drug hypersensitivity. In some cases of severe headaches with associated symptoms, headaches potentially represent drug-induced aseptic meningitis. The reviewer recommends inclusion of headache as the most frequent adverse event and a Warning and Precaution statement for aseptic meningitis in labeling for rozanolixizumab to alert treating physicians for adequate risk mitigation.

7.7.3. Hypersensitivity Reactions

Issue

TEAEs related to hypersensitivity reactions and local reactions at the site of administration were frequently observed in the subjects treated with rozanolixizumab in the Studies MG0003, MG0004, and MG0007.

Background

The topic of hypersensitivity reactions was of special interest as the Applicant's proposed label notes (b) (4).

Rozanolixizumab is a humanized anti-FcRn IgG4 monoclonal antibody that will be administered as a subcutaneous infusion. Like other monoclonal antibodies ([Isabwe et al. 2018](#); [Pintea et al. 2021](#)), rozanolixizumab treatment may potentially lead to an increase in hypersensitivity reactions and local reactions at the site of administration.

Assessment

In Study MG0003, subjects were observed at the study site for at least 4 hours following the first two infusions, and then 2 hours for subsequent infusions. In the open-label chronic weekly administration Study MG0004, subjects were observed at the study site for at least four hours following the first two infusions, and then two hours for subsequent infusions until Week 7, and afterwards at least 1 hour at the investigator's discretion. In the open-label cyclical treatment Study MG0007, subjects were observed for at least 1 hour following the first two infusions, and then a minimum of 15 minutes for subsequent infusions.

Anaphylactic Reactions

In Study MG0003, no TEAEs met the criteria for potential anaphylactic reactions during the double-blind treatment cycle. Similarly, in Safety Pool S1 pooling the data from Studies MG0003, MG0004, and MG0007, no TEAEs met the criteria for anaphylactic reactions. In 120-day safety update dated February 3, 2023, eCTD Sequence number 0012), a single nonserious

mild intensity TEAE of anaphylactic reaction to the bee sting and ant bite in the right upper extremity was reported that occurred 7 days after the last infusion of rozanolixizumab $\approx$ 10 mg/kg dose.

Hypersensitivity Reactions

[Table 63](#) shows the frequency of TEAEs of hypersensitivity reactions in the subjects treated with rozanolixizumab in the Study MG0003. Overall, seven (10.9%) subjects in the rozanolixizumab $\approx$ 7 mg/kg arm and eight (11.6%) subjects in the rozanolixizumab $\approx$ 10 mg/kg arm experienced symptoms and signs of hypersensitivity reactions compared with three (4.5%) subjects in the placebo arm. A majority of subjects experienced skin rash, erythema, and pruritis. One subject (MG0003- (b) (6)) experienced swollen tongue the same day as the first infusion of rozanolixizumab $\approx$ 7 mg/kg dose and received cetirizine and paracetamol. The subject received prophylactic cetirizine for the remaining doses. The subject experienced a second episode of tongue swelling 4 days after the fourth infusion. Both events resolved within a day and the study treatment was unchanged. All hypersensitivity reactions occurred within 1 to 13 days after the recent rozanolixizumab infusion and were observed after a total of 1 through 6 infusions in a 6-weekly infusion treatment cycle. In Safety Pool S1, out of 196 subjects, 26 (13.3%) subjects experienced skin rash, 17 (8.7%) experienced erythema, and 9 (4.6%) and 3 (1.5%) had TEAEs of pruritis and urticaria, respectively. In 120-day safety update, 27 (14.4%) subjects had TEAEs mapping to the SMQ hypersensitivity including 12 (6.4%) subjects who experienced rash and 3 (1.6%) subjects who experienced urticaria. The TEAEs of hypersensitivity reactions were mild or moderate intensity. There were no severe or serious TEAEs. One subject (MG0003- (b) (6)) discontinued rozanolixizumab $\approx$ 10 mg/kg dose treatment due to pruritis in Study MG0003 (see Section [7.6.2.4](#)). The time of onset of pruritis was 29 days after the first infusion and 8 days after most recent fourth infusion. The Applicant determined the pruritis was likely related to rozanolixizumab because there was no alternative explanation and the reported de-challenge.

In the 120-day safety update (dated February 3, 2023, eCTD Sequence number 0012), the Applicant stated that across the rozanolixizumab program, one subject with idiopathic thrombocytopenic purpura in study TP0006 reported serious urticaria of severe intensity 46 days after the first and fourth day after the most recent rozanolixizumab infusion.

Administration Site Reactions

[Table 63](#) shows the frequency of TEAEs of administration site reactions in the subjects treated with rozanolixizumab in the Study MG0003. Overall, four (6.2%) subjects in the rozanolixizumab $\approx$ 7 mg/kg arm and six (8.7%) subjects in the rozanolixizumab $\approx$ 10 mg/kg arm experienced symptoms and signs of administration site reactions compared with two (3%) subjects in the placebo arm. The TEAE symptoms included skin rash, redness, itching, pain, discomfort, inflammation, and bruising, with each category occurring in mostly one subject. These administration site reactions occurred within 1 to 3 days after administration and were observed after a total of 1 through 6 infusions in a 6-weekly infusion treatment cycle. In Safety Pool S1, out of 196 subjects, 26 (13.3%) experienced TEAEs of administration site reactions. There was no change in the number of subjects with TEAEs of administration site reactions in

the 120-day safety update. All TEAEs were graded as mild. There were no severe or serious TEAEs.

Table 63. Subjects With TEAEs of Hypersensitivity Reactions and Local Reactions at the Site of Administration, Safety Population, Study MG0003

Preferred Term	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈10 mg/kg N=69 n (%)
Hypersensitivity reactions			
Any reaction	3 (4.5)	7 (10.9)	8 (11.6)
Rash	0	3 (4.7)	3 (4.3)
Rash erythematous	0	0	1 (1.4)
Rash papular	2 (3)	1 (1.6)	1 (1.4)
Erythema	1 (1.5)	1 (1.6)	1 (1.4)
Pruritus	0	0	2 (2.9)
Eczema	0	1 (1.6)	0
Swollen tongue	0	1 (1.6)	0
Flushing	0	1 (1.6)	0
Administration site reactions			
Any reaction	2 (3)	4 (6.2)	6 (8.7)
Injection site rash	0	2 (3.1)	0
Injection site erythema	0	1 (1.6)	0
Injection site inflammation	0	1 (1.6)	0
Injection site reaction	0	1 (1.6)	0
Injection site discomfort	0	0	1 (1.4)
Injection site urticaria	1 (1.5)	0	0
Application site erythema	0	0	1 (1.4)
Application site pruritus	0	0	1 (1.4)
Infusion site erythema	0	1 (1.6)	1 (1.4)
Infusion site pain	0	0	1 (1.4)
Infusion site bruising	1 (1.5)	0	1 (1.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

Coded as MedDRA preferred terms.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event

The reviewer notes that pyrexia was one of the most common TEAEs in the subjects receiving rozanolixizumab. In Study MG0003, 15 (21.7%) subjects in the rozanolixizumab ≈10 mg/kg arm and 8 (12.5%) subjects in the rozanolixizumab ≈7 mg/kg arm experienced fevers compared with 1 (1.5%) in the placebo arm. Most fever events occurred within 4 days (mean 2.7 days) after rozanolixizumab infusion and lasted for the average of 1.2 days (range 0 to 4 days). All events were considered mild or moderate intensity and resolved without sequelae. The reviewer cannot rule out drug hypersensitivity as a potential cause for fevers in the subjects when no other cause of fever was evident after clinical and laboratory investigation.

Conclusion

The TEAEs of hypersensitivity reactions including skin rash, pruritis, swollen tongue, and flushing, as well as administration site reactions such as rash, redness, inflammation, itching, pain, and discomfort, were frequently observed in rozanolixizumab treated subjects in Studies MG0003, MG0004, and MG0007. There were no severe or serious TEAEs, or anaphylactic reactions reported during these studies. One subject discontinued rozanolixizumab due to a hypersensitivity reaction (pruritis).

The reviewer recommends that hypersensitivity reactions should be included in Warnings and Precautions. The label for a related drug, efgartigimod, has a Warning and Precaution for hypersensitivity reactions. The reviewer notes that hypersensitivity reactions are often unpredictable and can potentially lead to serious outcomes such as hypotension, anaphylaxis, or death. A Warnings and Precautions statement will help alert providers to this risk.

7.7.4. Gastrointestinal Disorders

Issue

TEAEs related to gastrointestinal (GI) disorders including diarrhea, nausea, and vomiting were frequently observed in the subjects treated with rozanolixizumab in the Studies MG0003, MG0004, and MG0007. These GI disorders TEAEs were also considered adverse events of special interest during these studies.

Background

The Applicant's proposed label notes that diarrhea was one of the most common adverse reactions ($\geq 10\%$) and other GI symptoms such as nausea and (b) (4) were more frequently reported aEs ($\geq 5\%$) in the subjects treated with rozanolixizumab compared to placebo in clinical studies.

Assessment

[Table 64](#) shows that in Study MG0003, the TEAEs of diarrhea, nausea, vomiting, and abdominal pain were reported in $\geq 5\%$ of subjects treated with rozanolixizumab and occurred more frequently in the rozanolixizumab arm than the placebo arm. The TEAE of diarrhea was more common in the rozanolixizumab ≈ 7 mg/kg arm (25%) compared to rozanolixizumab ≈ 10 mg/kg arm (15.9%) and placebo arm (13.4%). The majority of these GI disorders TEAEs were graded as nonserious events of mild or moderate maximum intensity. Two (3.1%) subjects in the rozanolixizumab ≈ 7 mg/kg arm experienced serious TEAEs of severe vomiting (n=1) and gastritis (n=1) which led to temporary drug discontinuation. Two (2.9%) subjects in the rozanolixizumab ≈ 10 mg/kg arm experienced nonserious TEAEs of vomiting and abdominal pain (n=1), and diarrhea (n=1) which led to discontinuation from study. The case narratives are described below.

Table 64. Treatment-Emergent Adverse Events¹ of Gastrointestinal Disorders in ≥5% of Subjects Treated With Rozanolixizumab and More Frequently Than Placebo Group, Safety Population, Study MG0003

Preferred Term ³	Placebo N=67 n (%)	RLZ≈7 mg/kg N=64 n (%)	RLZ≈10 mg/kg N=69 n (%)
Diarrhea	9 (13.4)	16 (25.0)	11 (15.9)
Nausea	5 (7.5)	5 (7.8)	8 (11.6)
Abdominal pain ⁴	4 (6.0)	6 (9.4)	5 (7.2)
Vomiting	1 (1.5)	2 (3.1)	4 (5.8)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final rozanolixizumab dose.

²Duration is 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks.

³Coded as MedDRA preferred terms.

⁴Includes abdominal discomfort, abdominal pain upper, and flank pain

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab.

The case narratives of two subjects who experienced serious TEAEs of vomiting and gastritis leading to temporary treatment discontinuation in the rozanolixizumab ≈7 mg/kg arm are described below (source: Module 5.3.5.1. mg0003-narratives):

- Subject MG0003/ (b) (6): 60-year-old male experienced serious TEAEs of vomiting and MG exacerbation 3 days after the first infusion of rozanolixizumab ≈7 mg/kg dose in Study MG0003. The subject presented to the emergency room with nausea, vomiting, and diarrhea along with severe MG exacerbation symptoms including worsening speech pronunciation, droopy eyelids, and shortness of breath. The subject threw up his usual dose of pyridostigmine with vomiting. The subject was hospitalized and placed on supplemental oxygen without a need for further ventilation. The subject had a fever (39.1°C) and oxygen saturation of 90s. Complete blood count was notable for total leukocyte count increased from 10.9 to 14.7 in 2 days (unit and range not reported) and comprehensive metabolic panel showed glucose 193 (unit and range not reported). An x-ray of the chest showed increased central interstitial markings and pulmonary edema versus atypical infection. The subject had a negative COVID-19 antigen test result. The subject was diagnosed with aspiration pneumonia of mild intensity. The subject was treated with pyridostigmine for MG, albuterol with ipratropium, ceftriaxone, metronidazole, and magnesium sulfate in dextrose for pneumonia aspiration, and metronidazole and cefdinir for pneumonia/sepsis. The symptoms resolved 3 days after onset. The subject did not require rescue therapy for MG worsening. The subject completed five infusions of rozanolixizumab ≈7 mg/kg dose (missed the second dose) and then rolled into open-label Study MG0007. There was no reported repeated dose rechallenge. The serious TEAE of severe vomiting was likely related to rozanolixizumab.
- Subject MG0003/ (b) (6): 55-year-old male experienced a serious TEAE of gastritis 24 days after the first and third day after the fourth infusion of rozanolixizumab ≈7 mg/kg dose in Study MG0003. The subject was admitted to the emergency room with mild vomiting and nonspecific chest pain due to gastritis and gastroesophageal reflux disease (GERD). The subject was treated with ketorolac and discharged after 23 hours. The Applicant stated in the case narrative that the laboratory test results, electrocardiogram, and imaging confirmed that chest pain was nonspecific and due to pre-existing condition of GERD. The laboratory tests provided in the case narrative were within reference range for complete blood count, liver

enzymes, procalcitonin, and troponin levels. The study drug was temporarily interrupted due to the TEAE of gastritis. The subject completed five infusions and rolled onto open-label Study MG0004. There was no reported repeated dose rechallenge. The serious TEAE of mild gastritis was likely related to rozanolixizumab.

The case narratives of two subjects who experienced nonserious TEAEs of vomiting, abdominal pain, and diarrhea leading to permanent treatment discontinuation in the rozanolixizumab ≈ 10 mg/kg arm are described below (source: Module 5.3.5.1. mg0003-narratives):

- Subject MG0003/ (b) (6): 41-year-old female experienced nonserious TEAEs of upper abdominal pain (epigastric pain) and vomiting 4 days after the first infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0003. The subject received hyoscine and tiquizium for the upper abdominal pain and domperidone and metoclopramide for the vomiting on the same day as the second infusion of rozanolixizumab. The symptoms resolved 19 days after onset and 16 days after the last dose of rozanolixizumab. The Applicant noted that the subject received the second dose of rozanolixizumab despite the investigator considering the TEAEs of abdominal pain and vomiting related to rozanolixizumab. The subject received treatment for the TEAEs after receiving the second dose of rozanolixizumab. The subject discontinued from the study and did not enroll into either of the open-label Studies MG0004 or MG0007.
- Subject MG0003/ (b) (6): 67-year-old male experienced a nonserious TEAE of severe diarrhea 2 days after the first infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0003. The subject reported Grade 3 diarrhea, cramping abdominal pain, and fever (38.3°C) 20 hours after the rozanolixizumab administration. The subject did not have vomiting or jaundice. The subject self-treated his symptoms with paracetamol at home. The subject had persistent diarrhea described as at least 10 episodes of loose stools without blood or mucus or undigested fats in the stools over 2 days. The subject received unspecified treatment in the emergency room and later hospitalized for diarrhea. The hospital workup excluded any condition which could have caused diarrhea. Laboratory test results (units and normal ranges not reported) revealed leucocyte count 14, C-reactive protein level 9, and bilirubin level 30. On day 4 after symptom onset, laboratory test results (units and normal ranges not reported) revealed sodium level 138, potassium level 3.8, chloride level 101, glucose level 5.1, urea level 7, creatinine level 111, bilirubin level 23, albumin 41, alanine aminotransferase 0.82, aspartate aminotransferase 0.39, gamma-glutamyl transferase 0.75, amylase 0.51, lipase 0.25, differential leucocytes 13.5, and no other significant abnormalities were noted. On the same day, an abdominal ultrasound revealed nonsignificant hepatosteatosis, and no other relevant findings or signs of cholecystopathy were noted. A stool culture was not performed. The immunoglobulin E predose was increased. The subject received natrium and a combination of fempiverinium with metamizole and pitofenone as treatment medications for the diarrhea. The event of diarrhea resolved 6 days after onset. Rozanolixizumab treatment was withdrawn due to diarrhea. The subject had a mild episode of diarrhea 5 months after the last dose of rozanolixizumab. The TEAE of diarrhea was likely related to rozanolixizumab.

[Table 65](#) shows the frequency of the GI disorders TEAEs including diarrhea, abdominal pain, nausea, and vomiting in the Safety Pool S1 comprising pooled data from Studies MG0003, MG0004, and MG0007. Overall, 89 (45.4%) subjects out of 196 subjects experienced GI disorders TEAEs with the frequency of the aEs balanced between rozanolixizumab $\approx$ 7 mg/kg and $\approx$ 10 mg/kg dose arms. The TEAE of diarrhea was the most common (31.6%) followed by nausea (16.8%), abdominal pain (15.3%), and vomiting (7.7%). Most TEAEs were of mild or moderate maximum intensity. There were no severe or serious TEAEs in the open-label Study MG0007. There were no treatment interruptions or discontinuation due to the GI TEAEs in Study MG0007. Overall, the incidence of the GI events remained similar with repeated treatment cycles (CSR MG0007 and 120-day safety update eCTD sequence number 0012). The Applicant reported in their 120-day safety update that there were 23 new GI disorders TEAEs and consistent with the BLA, the most common TEAEs were diarrhea, nausea, and abdominal pain.

Table 65. Treatment-Emergent Adverse Events of Gastrointestinal Disorders in $\geq$ 5% of Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

System Organ Class Grouped Query	RLZ $\approx$ 7 mg/kg N=95 n (%)	RLZ $\approx$ 10 mg/kg N=101 n (%)	RLZ Total N=196 n (%)
Gastrointestinal disorders (SOC)	45 (47.4)	44 (43.6)	89 (45.4)
Diarrhea	30 (31.6)	32 (31.7)	62 (31.6)
Abdominal pain	14 (14.7)	16 (15.8)	30 (15.3)
Nausea	14 (14.7)	19 (18.8)	33 (16.8)
Vomiting	6 (6.3)	9 (8.9)	15 (7.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as: MG0003— as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004— as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007— defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004— first 6 weeks of all study subjects, MG0007— is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Abdominal pain contains: Abdominal discomfort, Abdominal pain, Abdominal pain upper, Abdominal distension, Abdominal pain lower, Flank pain

Diarrhea contains: Diarrhea, Frequent bowel movements

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab; SOC, system organ class

Conclusion

The TEAEs of GI disorders including diarrhea, vomiting, nausea, and abdominal pain were frequently observed in the subjects receiving rozanolixizumab during the Studies MG0003, MG0004, AND MG0007. The event of diarrhea was the most common TEAE in rozanolixizumab treated subjects. A majority of these TEAEs were nonserious and of mild or moderate maximum intensity; however, there were also serious and severe GI events which resulted in the emergency room visit, hospitalization, treatment interruptions and study discontinuation.

7.7.5. Hypoalbuminemia

Issue

TEAE of hypoalbuminemia was observed in the rozanolixizumab treated subjects in the Studies MG0003, MG0004, and MG0007.

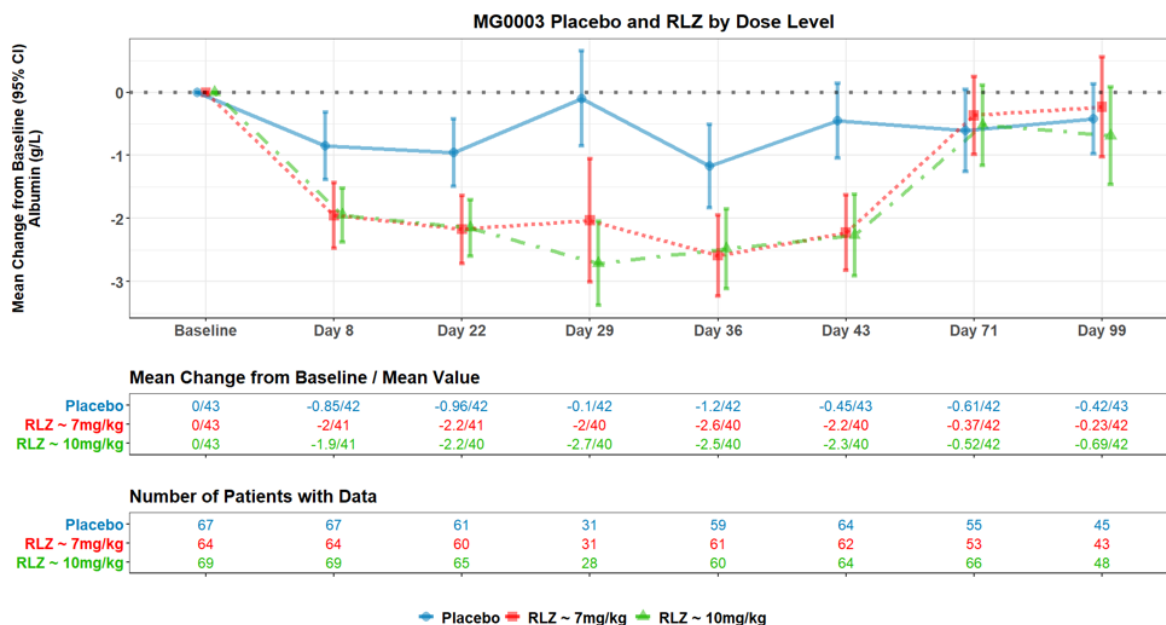
Background

The proposed mechanism of rozanolixizumab action is to inhibit the activity of neonatal Fc receptor (FcRn) and accelerate the catabolism of IgG, including MG-specific autoantibodies. The FcRn has affinity for both IgG and albumin, the two most abundant plasma proteins accounting for 80% to 90% of total protein pool. The FcRn plays an important role in the homeostatic regulation of IgG and albumin. Therefore, the topic of hypoalbuminemia was of special interest in this review.

Assessment

In Study MG0003, there was a mean decrease in serum albumin levels from baseline to day 43 of -2.2 g/L in the rozanolixizumab $\approx$ 7 mg/kg arm and -2.3 g/L in the rozanolixizumab $\approx$ 10 mg/kg arm compared to -0.45 g/L in the placebo arm (see [Figure 11](#); also refer to Section [7.6.2.6](#)). The decrease in mean albumin levels were observed from the first post baseline visit on day 8 and the mean albumin levels remained persistently lower in the rozanolixizumab-treated subjects compared to placebo throughout the treatment period. The albumin levels recovered to the placebo levels on day 71 during the observation period. The maximum lowest albumin value was 2.9 g/L in one subject receiving rozanolixizumab $\approx$ 10 mg/kg dose at day 99, the last day in the observation period (see Section [7.6.2.6](#)). None of the subjects had serum albumin levels lower than 2.5 g/L in the Study MG0003.

Figure 11. Mean Serum Albumin Levels Change From Baseline Over Time, Safety Population, Study MG0003



Source: ad b.xpt; Software: R

Note: Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
Abbreviations: RLZ, rozanolixizumab

In the OLE Study MG0007, the mean reductions in the serum albumin levels ranged between - 2.7 g/L (cycle 6, day 43) and -1.1 g/L (cycle 5, day 43) in the rozanolixizumab $\approx$ 7 mg/kg arm and between -3.3 g/L (cycle 7, day 15) and -0.5 g/L (cycle 5, day 15) in the rozanolixizumab $\approx$ 10 mg/kg arm (CSR MG0007). None of the subjects had serum albumin levels lower than 3.1 g/L during any of the repeat treatment cycles (Table 66). In 120-day safety update (eCTD sequence number 012), the Applicant stated that there were minimal (around 5%) reductions in albumin levels during treatment period which were not considered clinically meaningful in subjects treated with rozanolixizumab.

Table 66. Subjects With Low Serum Albumin Levels Meeting Specified Levels, Safety Population, Study MG0007

	RLZ Total Cycle 1 N=157	RLZ Total Cycle 2 N=157	RLZ Total Cycle 3 N=157	RLZ Total Cycle 4 N=157	RLZ Total Cycle 5 N=157	RLZ Total Cycle 6 N=157	RLZ Total Cycle 7 N=157	RLZ Total Cycle 8 N=157
Laboratory Parameter	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
Albumin, low (g/dL)								
Level 1 (<3.1)	0/153 (0)	0/118 (0)	0/93 (0)	0/70 (0)	0/46 (0)	0/26 (0)	0/10 (0)	0/1 (0)
Level 2 (<2.5)	0/153 (0)	0/118 (0)	0/93 (0)	0/70 (0)	0/46 (0)	0/26 (0)	0/10 (0)	0/1 (0)
Level 3 (<2)	0/153 (0)	0/118 (0)	0/93 (0)	0/70 (0)	0/46 (0)	0/26 (0)	0/10 (0)	0/1 (0)

Source: ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; RLZ, rozanolixizumab

Conclusion

Whereas reduction in the serum albumin levels were reported with rozanolixizumab treatment, these reductions (up to $\approx 5\%$ of baseline value) were not clinically significant in the subjects with gMG.

7.7.6. Immunization

Issue

The draft label has a section on immunization with vaccines.

Background

Treatment with rozanolixizumab is associated with increased risk of infections and reductions in the serum IgG levels. Refer to Section [7.7.1](#) for further details.

The Applicant has submitted the following language in the draft label:

(b) (4)

Assessment

Subjects who had received a live vaccination within 8 weeks before baseline visit or intended to have a live vaccination during the course of the Study or within 8 weeks following the final dose of study medication were excluded from the Studies MG0003, MG0004, MG0007. The reviewer notes that insufficient data are submitted by the Applicant to support safety of immunization with any vaccine during treatment with rozanolixizumab. Because treatment with rozanolixizumab is associated with reductions in serum IgG levels and increased frequency of infections, the reviewer agrees that the safety of immunization with live-attenuated or live vaccines and the response to immunization with any vaccine is unknown during treatment with rozanolixizumab, and that patients should be vaccinated with age-appropriate vaccinations according to immunization guidelines before starting treatment with rozanolixizumab.

Conclusion

Because treatment with rozanolixizumab is associated with reductions in serum IgG levels and increased frequency of infections, a Warnings and Precautions statement in labeling can help highlight that the safety of immunization with live-attenuated or live vaccines and the response

to immunization with any vaccine is unknown during treatment with rozanolixizumab, and that patients should be vaccinated with age-appropriate vaccinations according to immunization guidelines before starting treatment with rozanolixizumab.

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. Although patients with hepatic impairment were allowed to enroll in Study MG0003, no data are available to allow identification and classification of hepatically impaired patients based on Child-Pugh criteria.

Rozanolixizumab is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids. Further, markers of hepatic function, e.g., total bilirubin, ALT, AST, ALP were evaluated as potential covariates in the population pharmacokinetic (PK)/PD analysis but were not found to influence the final population PK/PD model parameters (Section [14.5.2.3](#), [Figure 34](#)).

As a result, hepatic impairment is not expected to affect rozanolixizumab clearance, 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 stated that patients with mild to moderate renal impairment were allowed to enroll in the clinical program. Per the Applicant, based on population PK/PD analyses, which included subjects with mild and moderate renal impairment, eGFR (range: 38.2 to 161 mL/min/1.73m²) did not significantly impact rozanolixizumab clearance. There are no data on the impact of severe renal impairment on PK of rozanolixizumab. As rozanolixizumab is a monoclonal antibody (with molecular weight >69 kDa), it is not expected to undergo renal elimination or excretion and thus no dosage adjustment is necessary for rozanolixizumab in patients with renal impairment.

Other Intrinsic Factors

The population PK analyses indicated that rozanolixizumab PK was not affected by age range: (range 18 to 89 years) and sex (57.5% female). For race, the phase 1 Study (UP0060) enrolled Chinese, Japanese, and Caucasian subjects who received single doses of rozanolixizumab at 4 mg/kg, ≈7 mg/kg or ≈10 mg/kg. In this study, compared to the Caucasians, lower exposures were observed in Chinese and Japanese subjects. This can be attributed to the lower body weight of Chinese and Japanese subjects, thus leading to lower actual dose (mg). However, after accounting for the body weight differences across Chinese, Japanese, and Caucasian populations, exploratory population PK/PD analysis revealed that ethnicity was not a significant covariate to affect PK or PD of rozanolixizumab. In the final population PK/PD analyses, due to small

number of patients in individual ethnic categories, the subjects were grouped as either Asian or non-Asian. The Applicant noted that no significant differences in rozanolixizumab clearance (CL)/fraction absorbed) F or V/F or in the total IgG or anti-AChR parameters of the models were found between Asian and Non-Asian subjects. Thus, the Applicant recommends that no dose adjustments are warranted based on these factors (Section [14.5](#)), and the review team agrees with that recommendation.

Body weight was found to be significant covariate to affect PK of rozanolixizumab. Refer to the Pharmacometrics review for additional discussion on effect of body weight on PK and PD of rozanolixizumab.

8.2. Extrinsic Factors

8.2.1. Drug Interactions

8.2.1.1. Effect of Other Drugs on Rozanolixizumab

Rozanolixizumab 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. Rozanolixizumab 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 at pH of 7.4, rozanolixizumab K_D (dissociation constant) was 55pM for human FcRn, likely indicating efficient FcRn blockage as binding of rozanolixizumab already occurs at the cell surface without the competition of endogenous IgG that is unable to bind FcRn at neutral pH. Further, rozanolixizumab was reported to bind human FcRn expressed at cell surface in Madin-Darby Canine Kidney ($K_D=0.43$ nM at pH 7.4).

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

8.2.1.2. Effect of Rozanolixizumab on Other Drugs

Rozanolixizumab 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, likely to result in reduced effectiveness of these moieties, if administered concomitantly.

The Applicant noted that approximately two weeks after the last of six weekly subcutaneous infusions of rozanolixizumab ≈ 7 mg/kg or ≈ 10 mg/kg, total IgG levels start returning towards baseline, while rozanolixizumab concentrations were mostly below the limit of quantitation

observed at the end of the infusion (seven days post-dose). Based on these data, the Applicant states that 2 weeks after the last infusion, IgG catabolism is no longer meaningfully affected by rozanolixizumab 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 rozanolixizumab infusion. If possible, the Applicant recommends postponing the start of treatment with a therapeutic moiety noted above until two weeks after the last rozanolixizumab dose is administered.

The review team acknowledges that the total IgG levels start to increase after the last of six weekly subcutaneous infusions of rozanolixizumab ≈ 7 mg/kg or ≈ 10 mg/kg, but they return to baseline levels approximately nine weeks after the last (sixth) infusion of rozanolixizumab. Therefore, the rationale for Applicant's recommendation to postpone the initiation of treatment with a therapeutic moiety noted above until 2 weeks after the last rozanolixizumab dose is administered, is unclear.

The review team recommends close monitoring for reduced effectiveness of therapeutic moieties that bind to FcRn such as those noted above when concomitant use is necessary. However, when long-term use of medications is necessary for patient care, the review team recommends stopping rozanolixizumab and using alternative medications to treat gMG. Furthermore, minimal reductions in albumin were observed during rozanolixizumab treatment (phase 3 study) which were not clinically meaningful. Therefore, rozanolixizumab is not expected to have a clinically relevant effect on the disposition of highly protein-bound drugs.

Immunizations

Immunization with vaccines during rozanolixizumab 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 and vaccination with live-attenuated or live vaccines is not recommended during treatment with rozanolixizumab.

8.3. Plans for Pediatric Drug Development

Not applicable. Rozanolixizumab was granted orphan drug designation. Pediatric assessments under the Pediatric Research Equity Act are not required.

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

There are limited data for the use of rozanolixizumab in pregnant and lactating women because the subjects of childbearing potential were required to use a highly effective method of birth control and study drug was discontinued if they became pregnant as per the protocol. There was one subject MG0004/ (b) (6) in the open-label Study MG0004 who gave birth to a full-term healthy child after 4-weeks exposure to rozanolixizumab ≈ 7 mg/kg dose in the first trimester of pregnancy. Rozanolixizumab was discontinued after a positive pregnancy test. The subject had an SAE of MG crisis 39 days after the last dose of rozanolixizumab, which resolved

4 days after onset with IVIg therapy. She had received placebo in the double-blind controlled Study MG0003.

9. Product Quality

Approval With Postmarketing Commitments

Rozanolixizumab is a recombinant, humanized antineonatal Fc receptor (FcRn) immunoglobulin G4 monoclonal antibody with amino acid substitution at serine (b) (4) to proline (IgG4P) to prevent Fab arm exchange characteristic of endogenous human IgG4. Rozanolixizumab is produced in Chinese hamster ovary DG44 cell line by recombinant DNA technology. The approximate molecular weight is 148 kDa.

Rystiggo (rozanolixizumab-noli) injection is supplied as a sterile, preservative-free, colorless to pale brownish yellow, clear to slightly opalescent solution for subcutaneous injection. Each vial contains 2mL of rozanolixizumab at a nominal formulation of 140 mg/mL in (b) (4) L-histidine hydrochloride monohydrate, (b) (4) mM L-proline, (b) (4) % (w/v) polysorbate 80, at pH 5.6.

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761286 for Rystiggo manufactured by UCB, Inc. for human use under conditions specified in the package insert. The data submitted in this application are adequate to support the conclusion that the manufacture of Rystiggo is well-controlled and leads to a product that is pure and potent.

The chemistry, manufacturing, and controls postmarketing commitments to be included in the action letter are listed below.

CMC PMC #1

To develop a two-tiered reference standard system consisting of primary and working reference standards to support the rozanolixizumab product lifecycle. The primary and working reference standard will be created from representative DS batches which have passed all release specifications. The first new reference standards will be qualified against the current reference standard (b) (4) according to a predefined protocol. The results for qualification of new primary and working/secondary reference standards will be submitted in a Prior Approval Supplement. Alternatively, protocols for qualification and requalification of future primary and working/secondary reference standards may be submitted as a Prior Approval Supplement, which may facilitate a reduced reporting category for implementation of new reference standards. Final reference standard qualification report submission date: 02/29/2024

CMC PMC #2

To perform a shipping validation study under real time shipping conditions (i.e., temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using rozanolixizumab finished product in the final commercial container closure and packaging systems to verify the impact of shipping on the product quality of rozanolixizumab finished product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

9.1. Device or Combination Product Considerations

Not applicable.

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

The results of the clinical site inspections support the conclusion that the studies were conducted adequately, and that the data generated support the proposed indication. Review of the financial disclosures did not raise concerns about the validity or reliability of the data.

11. Advisory Committee Summary

Not applicable.

III. Additional Analyses and Information

12. Summary of Regulatory History

Rozanolixizumab was developed by Union Chimique Belge (UCB) under investigational new drug (IND) 132407 for the treatment of myasthenia gravis (MG) in adults. In the Division's December 9, 2016, pre-IND written responses, the Division responded to the Sponsor's interest in developing a patient-reported outcome (PRO) assessment that would be used to evaluate treatment benefit directly from the patients' perspective for use as a secondary endpoint (b) (4). The Division agreed with the core concepts of the PRO but was concerned with the validity of the PRO instrument (b) (4).

The IND was submitted to the Agency on February 28, 2017. Initial reviews described rozanolixizumab as a recombinant, humanized, neonatal Fc receptor (FcRn) immunoglobulin (Ig) G4P monoclonal antibody. The Applicant stated that a first-in-human study (UP0018) was conducted and completed in the United Kingdom and there was an ongoing study in patients with immune thrombocytopenia (ITP) (TP0001) in the European Union and Australia. Therefore, the initial IND proposed a phase 2a clinical study (MG0002) in subjects with moderate to severe generalized MG. The study was allowed to proceed on March 29, 2017. Rozanolixizumab was granted orphan drug designation on February 1, 2019, for the treatment of gMG.

At the end-of-phase-2 meeting, discussions focused on the design and adequacy of the proposed phase 3 Study, MG0003 (minutes dated June 14, 2019), including the use of a novel MG symptoms PRO instrument (MGSPRO). The Division was concerned that the MG Symptoms PRO was not a clinically meaningful endpoint. A Type C Guidance meeting discussed patient-focused MG Symptoms PRO (minutes dated November 3, 2020). The Division reiterated their comments and concerns regarding the MG Symptoms PRO from the end-of-phase 2 meeting. The Division noted that (b) (4) would be a matter of review at the time of the biologics license application (BLA) submission.

A chemistry, manufacturing, and controls (CMC)-only meeting discussed key (b) (4) facility design features and concepts as well as obtained relevant good manufacturing practice input (minutes dated December 10, 2020). A Type C Guidance meeting discussed the proposed statistical analysis plan for the phase 3 Study, MG0003 (minutes dated December 22, 2020). The Division advised the Applicant to describe the statistical methodology used to estimate the treatment effect in detail. At the Model Informed Drug Development meeting, discussions focused on the use of a model-informed approach to support a switch from weight-tiered doses to a fixed dose of (b) (4) mg of rozanolixizumab in patients with generalized MG (gMG). The objective of the switch was to simplify dosing and reduce potential for dosing errors (minutes dated March 26, 2021). A Type C Guidance meeting discussed the integrated statistical analysis plan and development of the integrated summary of efficacy and integrated summary of safety to support the rozanolixizumab BLA (minutes dated November 10, 2021). The Division stated that at least half of the safety database should consist of patients dosed with the highest anticipated dose and

frequency of dosing planned for marketing. (b) (4)

the Division stated that they would consider these analyses to be exploratory. The Division stated that primary analysis of safety data should use the number of patients as the denominator.

In the pre-BLA meeting (minutes dated July 19, 2022), the Division recommended the Applicant request a CMC-only Type B Pre-BLA meeting to discuss the specific aspects of the CMC program. Additionally, the Division recommended that the Applicant include a statement of how they intend to meet the substantial evidence of effectiveness standard, provide subgroup analyses of the acetylcholine receptor antibody positive population and the muscle-specific kinase antibody positive population, and conduct the primary and secondary analyses on these two subgroups and include the analyses in their BLA submission.

Because rozanolixizumab for the treatment of 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.

BLA 761286 was submitted on October 24, 2022, and was filed on December 21, 2022, with no filing issues identified. This original BLA received priority review designation because of the potential benefit to the muscle-specific kinase antibody positive population; and was reviewed under “The Program.” The nonproprietary name suffix request was submitted on September 1, 2022. Rozanolixizumab was conditionally approved on March 27, 2023. The proprietary name review request was submitted on October 28, 2022, and found conditionally acceptable on January 13, 2023.

13. Pharmacology Toxicology

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

13.1.1. Pharmacology (Primary and Secondary)

Pharmacology

UCB7665 is a humanized immunoglobulin G (IgG) monoclonal antibody intended to suppress FcRn-mediated IgG recycling. In vitro studies using plasmon surface resonance and transfected Madin-Darby canine kidney (MDCK) cells indicated picomolar affinity of UCB7665 for both human and monkey FcRn. In vivo studies in transgenic mice that express human FcRn (i.e., hFcRNTg) indicated increased clearance of previously administered human IgG following single intravenous (IV) doses of 0, 10, 30, and 100 mg/kg UCB7665. Additionally, circulating IgG levels were reduced in male and female cynomolgus monkeys in the general toxicity studies in which subcutaneous (SC) doses of up to 150 mg/kg UCB7665 were administered every 3 days for up to 26 weeks.

Secondary Pharmacology

The potential for UCB7665 to stimulate cytokine release was investigated in in vitro studies using whole blood, human peripheral blood mononuclear cells (PBMC), human umbilical vein endothelial cells (HUVEC), whole blood with HUVECs, and PBMCs with HUVECs.

Four assay designs were used that assessed soluble UCB7665, UCB7665 immobilized on plates, UCB7665 cross-linked with an anti-human Fc F(ab')₂, and UCB7665 immobilized on beads. All assays, conducted using appropriate positive and negative controls, did not indicate the potential for stimulation of UCB7665-induced cytokine release.

Pharmacokinetics

Pharmacokinetic parameters were assessed following intravenous and SC administration of UCB7665 in the 4- and 13-week toxicology studies in cynomolgus monkeys. In both studies, anti-drug antibody (ADA) development in most animals was observed. The ADA response was generally correlated with reduced pharmacodynamic (PD) effect (i.e., a reduction in IgG levels) and reduced exposure in animals with higher ADA titers.

13.1.2. Safety Pharmacology

No stand-alone safety pharmacology studies were conducted. There were no test article-related effects on cardiovascular, neurobehavioral, or respiratory (no plethysmography) safety pharmacology parameters that were incorporated into the 4- and 13-week general toxicity studies.

13.1.3. Toxicology

13.1.3.1. General Toxicology

General toxicity studies of 4-, 13- and 26-weeks' duration were conducted in cynomolgus monkey administered up to 150 mg/kg UCB7665 by SC injection every 3 days. There was no serious toxicity. Drug-related findings consisted of reductions in globulin levels due to reduced IgG levels, which are expected based on the pharmacology of the drug. Accompanying the dose-related reductions in IgG were decreases in total protein and increased A/G ratio. In addition, a trend toward slightly reduced albumin was observed. Full recovery was observed by the end of the 8-week recovery period. Immunophenotyping was conducted and no test article-related changes in immune cell subtypes were observed.

An assessment of T-cell-dependent antibody response was conducted during the dosing period in the 13-week study. Although there was no effect on immunoglobulin M response, administration of UCB7665 resulted in inhibition of the IgG response to keyhole limpet hemocyanin (KLH); recovery was not assessed. Neutralizing anti-drug antibodies (ADAs) were detected in all dosed groups and ADA was greater in groups that received UCB7665 by SC injection.

13.1.3.2. Genetic Toxicology

No genetic toxicology studies were conducted.

13.1.3.3. Carcinogenicity

Based on a weight of evidence assessment, conduct of carcinogenicity studies were deemed not necessary for UCB7665.

13.1.3.4. Special Toxicology

Tissue Cross-Reactivity

Good Laboratory Practice-compliant tissue cross-reactivity studies were conducted in human and cynomolgus monkey tissues. The staining patterns were generally similar between species; however, the study report did not specify whether specific binding was membranous or cytoplasmic. Therefore, relevance of the binding in specific tissues for assessing safety is difficult to determine. However, the similarity of staining patterns between species supported use of the cynomolgus monkey for nonclinical testing.

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

13.2.1. Introduction

An enhanced pre- and postnatal development study in cynomolgus monkey was the only nonclinical study of UCB7665 submitted only to the NDA.

13.2.2. Key Findings

Subcutaneous administration of 0, 50, or 150 mg/kg UCB7665 every 3 days to pregnant female cynomolgus monkeys from gestational day (GD) 20 through parturition caused embryonic losses in 3 of 19 females at both doses.

Throughout the postnatal period, infant body weights in females were reduced at both doses. The immune function in infants was impaired at both doses.

There were no test article effects on maturation, neurobehavioral endpoints, or postmortem findings in offspring from postnatal day (PND) 7 through PND 180.

13.2.3. Enhanced Pre and Postnatal Development

Table 67. UCB7665 Enhanced Study for Effects on Pre- and Postnatal Development in Cynomolgus Monkeys With a Six-Month Postnatal Development Phase, Study Details

Study no:	NCD3001
Study report location:	DocuBridge, sequence 0001, 4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	22 NOV 2018
GLP compliance:	Yes, German Chemical Law and OECD
QA statement:	Yes
Drug, lot #, and % purity:	UCB7665, Batch No. 229448, 99.3% pure

Source: Applicant's Study NCD3001

Abbreviations: GLP, Good Laboratory Practice; OECD, Organisation for Economic Co-operation and Development; QA, quality assurance

Table 68. UCB7665 Enhanced Study for Effects on Pre- and Postnatal Development in Cynomolgus Monkeys With a 6-Month Postnatal Development Phase, Study Methods

Doses:	0, 50, 150 mg/kg/dose
Frequency of dosing:	Once every 3 days
Dose volume:	2 mL/kg
Route of administration:	Subcutaneous
Formulation/Vehicle:	Prepared before every fourth dose and refrigerated (5°C) Vehicle: (b) (4) mM Histidine, (b) (4) mM Proline, (b) (4) % Polysorbate [PS] 80, pH5.6
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3 groups of 19 pregnant females each
Satellite groups:	None
Study design:	Pregnant cynomolgus monkeys were administered 0, 50, or 150 mg/kg UCB7665 by subcutaneous (SC) injection every 3 days from gestational day (GD) 20 until birth. The doses were selected based on tolerance in 4, 13, and 26-week general toxicity studies, and were expected to result in saturation of PD effect (reduced IgG due to suppression of FcRn).
Deviation from study protocol:	No impact on the study results. Deviations in clinical observations were largely of minor differences in the times of examinations/observations or of delayed entry of findings into Pristima®. Clinical chemistry deviations were mostly due to inadequate sample volume or clotted samples from infants. Necropsy deviations were largely of missing tissues, altered fixation timing.

Source: Applicant's Study NCD3001

Abbreviations: FcRn, neonatal fragment crystallizable receptor; GD, gestational day, IgG, immunoglobulin G; PD, pharmacodynamic; PS, polysorbate, SC, subcutaneous

Observations and Results

F0 Dams

Mortality and Clinical Signs (Assessed at Least 1/day; Detailed Examinations Were Conducted Weekly)

- There were no test article-related clinical findings.

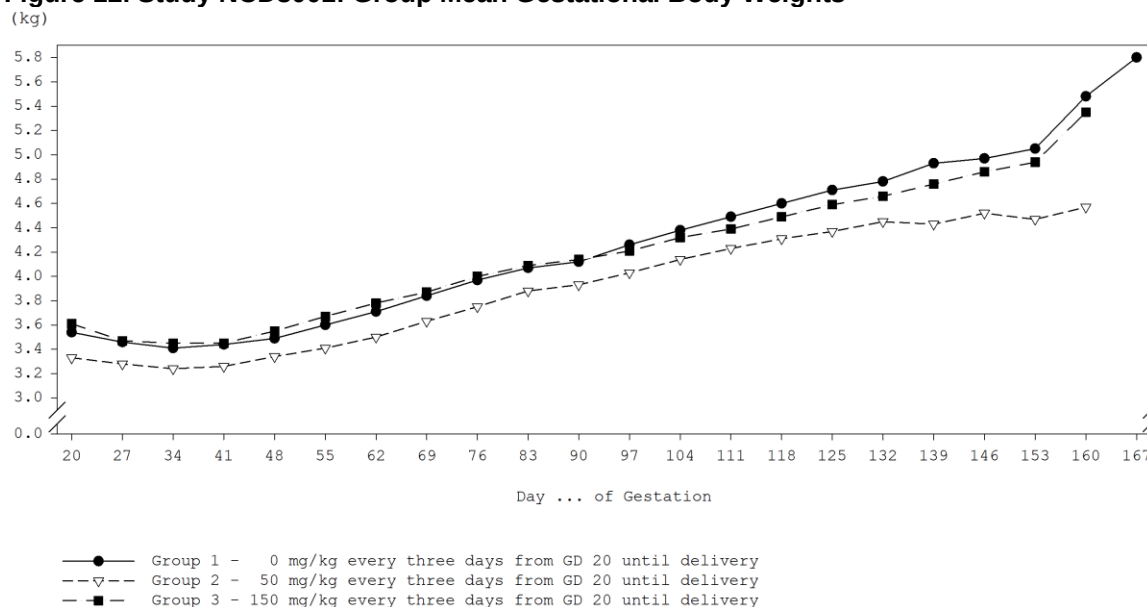
Body Weights

- Body weight was measured weekly from GD 20 until parturition, on lactational days 1 and 7, then weekly thereafter. Terminal body weight was assessed 24 hours prior to necropsy.

Gestational Body Weights

- No dose-related effects on gestational body weights were reported
- Body weights in the low density (LD) were consistently lower than control (C) and high density (HD)
- Differences between C and HD were not significant

Figure 12. Study NCD3001: Group Mean Gestational Body Weights



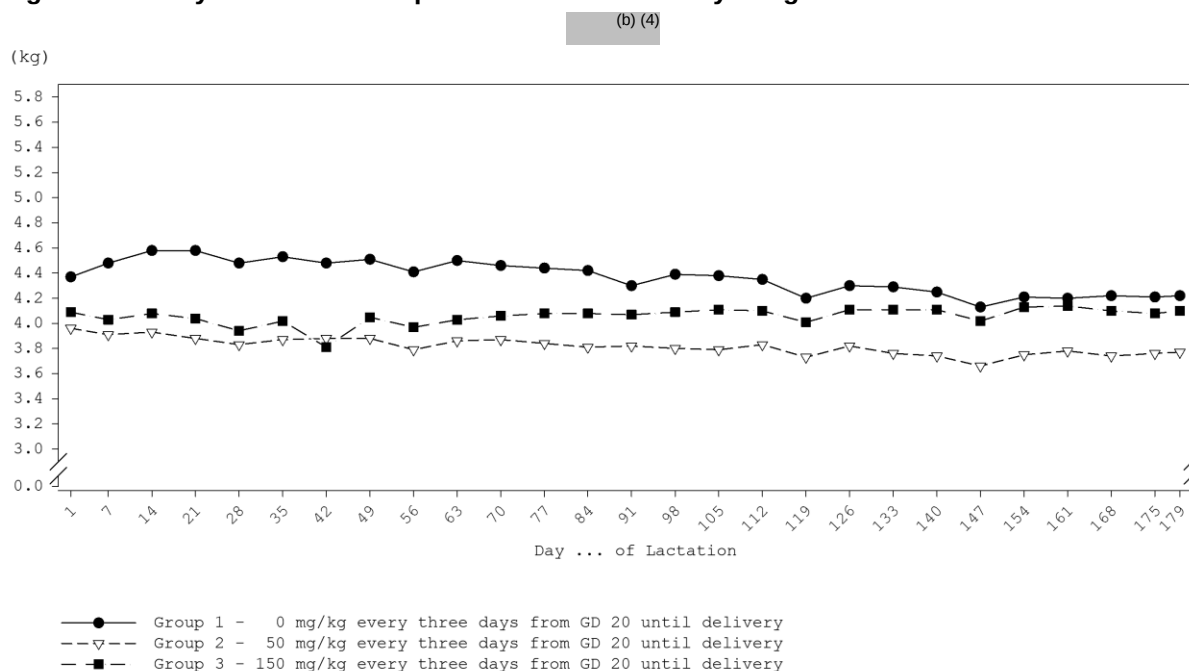
Source: Applicant's study report

Abbreviations: GD, gestational day

Lactational Body Weights

- Mean group body weights in the HD were initially lower than C but with no significant differences by lactation day 140.
- Lactational body weights in LD were consistently lower than C or HD.

Figure 13. Study NCD3001: Group Mean Lactational Body Weights



Source: Applicant's CSR.

Abbreviations: GD, gestational day

Body weights of animals that were maintained postpartum in social groups and no longer dosed (designated as Social Phase): No test article effects on body weights during the Social Phase were reported.

Food consumption was estimated once daily for each cage throughout the study

- No test item-related effects on food consumption during the gestation or lactation phase were reported.

Toxicokinetics (TK)

Blood samples for analyses of plasma concentrations or TK parameters were collected on GDs 20, 44, 59, 86, 110, and 143, and on LD 1, 7, and 28. TK parameters were assessed on GDs 44, 86, and 143. Increases in C_{max} and area under the curve (AUC) were greater than dose proportional and increased with repeat dosing.

Significant variability in plasma exposure was observed by GD 44, in which plasma concentration analysis in 11/16 laser Doppler flowmetry (LDF) indicated no detectable drug at 72 hours post dose. In contrast, a similar effect was only observed in 4/15 hemodiafiltration (HDF). Although the pharmacodynamic (PD) effect of UCB7665 (i.e., FcRn suppression) may have contributed to drug clearance, the higher variability in LDF was likely due to more extensive formation of neutralizing ADA relative to HDF.

In LDF and HDF, plasma concentrations on postpartum day (PPD) 1 were similar to those at GD 143 but were below the limit of quantification by PPD 7.

Table 69. T_{max} (h), C_{max} (µg/mL), and AUC_{tau} (µg*day/mL) on Days 44, 86, and 143 at Doses of 50 mg/kg and 150 mg/kg.

GD	50 mg/kg			150 mg/kg		
	T _{max} (h)	C _{max} (µg/mL)	AUC _{tau} (µg*day/mL)	T _{max} (h)	C _{max} (µg/mL)	AUC _{tau} (µg*day/mL)
44	8	112	132	24	972	1660
86	24	112	344	24	1080	2010
143	24	139	247	24	1500	3180

Source: Applicant's study report

Abbreviations: AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; GD, gestational day; T_{max}, time to maximum plasma concentration

Clinical Pathology

Blood samples were collected on GDs 20, 86, and 143 and on LD 7, 10, 28, 56, 119, 147, and 180.

No test article effects on hematology or coagulation parameters were reported.

Clinical Chemistry

IgG samples were collected on GD 20, 30, 44, 59, 86, 110 and 143, and on LD 7, 28, 42 and 56. Relative to controls, IgG levels were markedly reduced in both dosed groups throughout gestation.

Figure 14. Study NCD3001: IgG and Albumin Levels at GD 20 (Baseline) and Percent Change Through Gestation to LD 28

Group	GD 20	GD 44	GD 59	GD 86	GD 110	GD 143	LD 7	LD 28
IgG (g/L)		%						
0mg/kg	10.771	98.4	100.9	102.4	103.2	106.8	110.3	105.6
50mg/kg	10.875	39.2 ^c	35.0 ^c	34.6 ^c	33.4 ^c	34.2 ^c	58.7 ^c	110.1
150mg/kg	10.414	27.5 ^c	34.0 ^c	47.2 ^c	47.9 ^c	48.6 ^c	79.3 ^a	105.1
Albumin (g/L)		%						
0mg/kg	38.258	95.9	86.8	81.9	80.6	78.1	82.7	103.7
50mg/kg	39.661	87.2	76.9	72.2	69.8 ^a	66.6 ^b	76.6	99.5
150mg/kg	39.680	89.7	86.3	79.5	76.4	74.0	75.1	98.5

Source: Applicant's study report

^a P≤0.05. ^b P≤0.01. ^c P≤0.001.

Abbreviations: GD, gestation day; LD, lactation day

ADA developed in all dosed females. The ADA response was greater at the MD than the HD. Controls and those in the social phase did not have measurable ADA.

The Applicant specified that if abortion, fetal death, stillbirth, or infant loss occurred, the female remained in the “social phase” (remained caged with the social group) but was no longer part of the study. When the last cage mate was necropsied, the social phase animals were terminated, examined grossly, and organs fixed for possible histologic examination.

Table 70. Applicant's Table : ADA Responses of Maternal Females and Their Infants, Study NCD3001

Group 1 (0mg/kg)				Group 2 (50mg/kg)				Group 3 (150mg/kg)			
Animal	ADA Response	Infant	ADA Response	Animal	ADA Response	Infant	ADA Response	Animal	ADA Response	Infant	ADA response
P0016	low	P0016-1	low	P0101	mid	P0101-1	mid	P0201	mid	P0201-1	low
				P0102	high	P0102-1	high	P0202	low	P0202-1	low
				P0103	no			P0203	low		
				P0104	high	P0104-1	high	P0204	mid	P0204-1	low
				P0105	mid	P0105-1	mid	P0205	no		
				P0106	no			P0206	mid	P0206-1	low
				P0107	low			P0207	no		
				P0108	high	P0108-1	high	P0208	low		
				P0109	high	P0109-1	high	P0209	mid		
				P0110	low	P0110-1	low	P0210	low	P0210-1	low
				P0111	no			P0211	no		
				P0112	high	P0112-1	high	P0212	mid	P0212-1	mid
				P0113	high	P0113-1	high	P0213	low	P0213-1	low
				P0114	high	P0114-1	high	P0214	mid		
				P0115	mid	P0115-1	low	P0215	high	P0215-1	mid
				P0116	mid	P0116-1	high	P0216	low	P0216-1	low
				P0117	high	P0117-1	high	P0217	low	P0217-1	low
				P0118	mid	P0118-1	low	P0218	low	P0218-1	low
				P0119	mid	P0119-1	low	P0219	low		

ADA=Anti-Drug Antibody

Source: Applicant's Table (Study NCD3001)

Pregnancy Outcomes

There was a clear test article-related effect on embryonic loss. Three LD and three HD losses were documented by ultrasonography on GD 30 – after the first three doses. The females were placed in the social phase by GD 32 and prior to the first TK sampling.

Early fetal loss in a fourth HDF was not considered to be a test-article related effect. Ultrasonography showed that the fetus was alive and within group range of fetal size on GD 30. On GD 44, after surgery and medication, an intrauterine death was documented. Aborted material was found in the cage 16 days later; the animal was moribund and euthanized.

Table 71. Applicant's Table: Overview of Pregnancy Outcomes

Animals		Early Pregnancy Loss	Mid Pregnancy Loss	Late Pregnancy Loss	Loss At Birth	Infant Loss
Group: Dose	N	GD 20 to 50	GD 51 to 100	GD 101 to 175	PND 0	PND 1 to 7
1: 0mg/kg	19		P0010 GD 70		P0009-1	P0001-1 PND 3, P0005-1 PND 5, P0012-1 PND 5, P0017-1 PND 2, P0018-1 PND 1, P0019-1 PND 7
2: 50mg/kg	19	P0103 GD 30, P0106 GD 29, P0111 GD 31				P0105-1 PND 2, P0107-1 PND 2, P0110-1 PND 3, P0016-1 PND 4
3: 150mg/kg	19	P0205 GD 31, P0207 GD 31, P0211 GD 32, P0214 GD 45			P0203-1, P0208-1, P0209-1, P0219-1	

GD=Gestation Day; N = Number; PND=Postnatal Day.

Source: Applicant's table

Necropsy of Maternal Females

- Signed and dated pathology report: Yes
- Peer Review: Yes

At necropsy, a macroscopic exam was performed, and a standard list of organs were weighed.

An extensive list of organs was preserved in appropriate fixatives. Histologic examination was limited to femur, mammary gland, lymph nodes, CNS, spleen, bone marrow, thymus, and tonsils.

Animals in the social phase due to early fetal losses were examined macroscopically and organs weighed and fixed but not examined histologically.

Organ weights: No test article-related effects were reported.

Macroscopic Examination

- No test article-related effects were reported

Microscopic Examination

- No test article-related effects were reported.

F1 Generation

Table 72. Applicant's Summary Table (Study NCD3001): Infant Pregnancy Outcomes

Test Item	(dosage)	1	2	3
UCB7665	mg/kg every 3 days from GD 20 until delivery	0	50	150
Group/Sex:		1/F	2/F	3/F
Number of Pregnant Females:		19	19	19
Number of infants born		18	16	15
Number of infants stillborn		1	-	2
Number of infants live born		17	16	13
Number of infants with early delivery		2	2	4
Number of infants found dead on day 0 post-partum		-	-	2
Number of infants found dead on day 2 post-partum		1	2	-
Number of infants found dead on day 3 post-partum		1	1	-
Number of infants found dead on day 4 post-partum		-	1	-
Number of infants found dead on day 5 post-partum		1	-	-
Number of infants found dead on day 11 post-partum		-	-	1
Number of infants with accidental death on day 7 post-partum		1	-	-
Number of infants sacrificed moribund on day 1 post-partum		1	-	-
Number of infants sacrificed moribund on day 5 post-partum		1	-	-
Number of infants sacrificed moribund on day 17 post-partum		1	-	-
Number of male infants/fetus		9	8	9
Number of female infants/fetus		9	8	6
Sex ratio - Males (%)		50.0	50.0	60.0
Sex ratio - Females(%)		50.0	50.0	40.0
Number of male infants with terminal sacrifice		6	5	7
Number of female infants with terminal sacrifice		4	7	3

Source: Applicant's Summary Table (Study NCD3001)

Mortality

Early death at all doses was consistently associated with low birth weights (<300 g) and/or early parturition. A cause of death was determined for 5 of 8 Control and 1 of 5 HD infants.

Controls

- Found dead PND 3. Death considered related to a patent *foramen ovale* observed on macroscopic examination of the heart.
- Rejected at birth by maternal female and sacrificed as moribund on PND 5 with acute pulmonary inflammation.
- Severe bite wounds from the maternal female: infant was sacrificed moribund on PND 17.
- Sacrificed as moribund on PND 1. Upon macroscopic evaluation of the fixed heart, a patent *foramen ovale* and a description ("2 tips at the bottom") compatible with a double apex sign due to ventricular hypertrophy.
- Death was found to be the traumatic injury when caught in a fight between two maternal females

HD

- Found dead on PND 11. Very low birth weight (208 g) and failed to thrive. Based on macroscopic evidence of nasal skin erosions and scabs on the eyelids, the cause of death was determined to be related to trauma.

After macroscopic and microscopic examinations, a cause of death was not determined for the remaining infants.

Table 73. Applicant's Table (Study NCD3001): Individual Infant Mortality - Clinical Observations

	Animal Number	Fate	Day of Birth	Day of Death	Comments
Control group					
Stillborn	P0009-1 Female	Found dead		GD 160	
Live born	P0001-1 Male	Found dead	GD137	PND 3	Premature delivery (230g) Did not survive
Live born	P0005-1 Female	Sacrificed moribund	GD148	PND 5	Normal delivery (286g) No maternal care, did not survive although an attempt to hand raise it
Live born	P0012-1 Male	Found dead	GD156	PND 5	Normal delivery (285g)
Live born	P0014-1 Female	Sacrificed moribund	GD158	PND 17	Normal delivery (277g)
Live born	P0017-1 Male	Found dead	GD139	PND 2	Premature delivery (218g) Poor physical condition, discolored skin at different sites of the body
Live born	P0018-1 Female	Sacrificed moribund	GD145	PND 1	Normal delivery (232g) Poor physical condition, respiratory problems Sacrifice bad maternal care
Live born	P0019-1 Female	Found dead	GD159	PND 7	Normal delivery (253g) Death due to cage accident
50mg/kg					
Live born	P0105-1 Male	Found dead	GD 159	PND 2	Normal delivery (301g) Lesions and discolored parts of the body
Live born	P0107-1 Male	Found dead	GD 139	PND 2	Premature delivery (184g) Too low body weight to survive
Live born	P0110-1 Male	Found dead	GD 145	PND 2	Normal delivery (243g) Lesions
Live born	P0116-1 Female	Found dead	GD 157	PND 4	Normal delivery (272g)
150mg/kg					
Stillborn	P0208-1 Female	Found dead		GD 153	
Stillborn	P0209-1 Female	Found dead		GD 150	
Live born	P0203-1 Male	Found dead	GD 133	PND 0	Premature delivery (240g) Too low body weight to survive
Live born	P0217-1 Female	Found dead	GD 145	PND 11	Normal delivery (208g) Too low body weight to survive
Live born	P0219-1 Male	Found dead	GD 144	PND 0	Normal delivery (235g) Too low body weight to survive

Source: Applicant's Table (Study NCD3001)

Abbreviations: GD, gestational day, PND, postnatal day

Infant survivals beyond postnatal day 7 were similar among groups:

Table 74. Applicant's Table (Study NCD3001): Infant Survival From Birth Through Postnatal Day 180

Dose Level	0mg/kg	50mg/kg	150mg/kg
Number of live born infants	17	16	13
Number of infants found dead/sacrificed in a moribund condition	7	4	3
Number of live infants until PND 8	11	12	11
Number of live infants until PND 180	10	12	10
Infant survival index in percent (number alive at >PND 180/number live born x 100)	58.8%	75%	76.9%

PND=Postnatal Day.

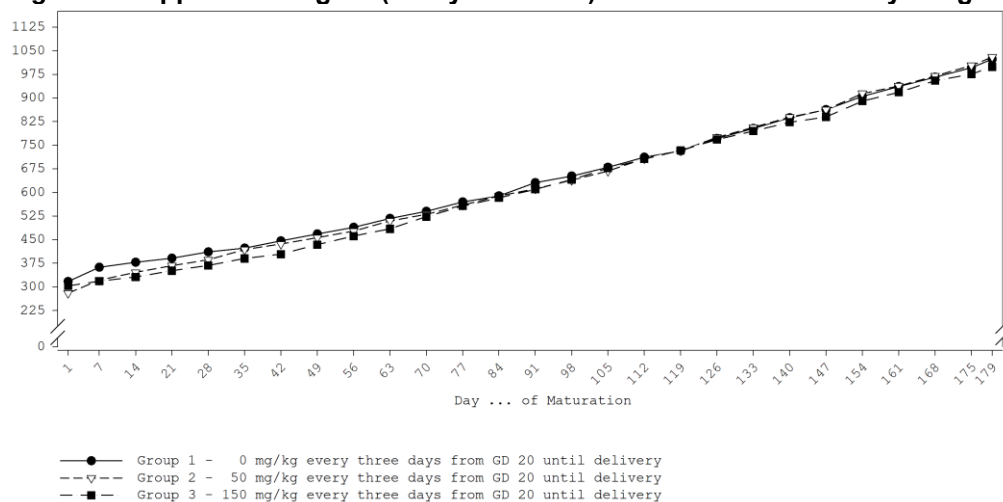
Source: Applicant's Table (Study NCD3001)

Clinical Signs

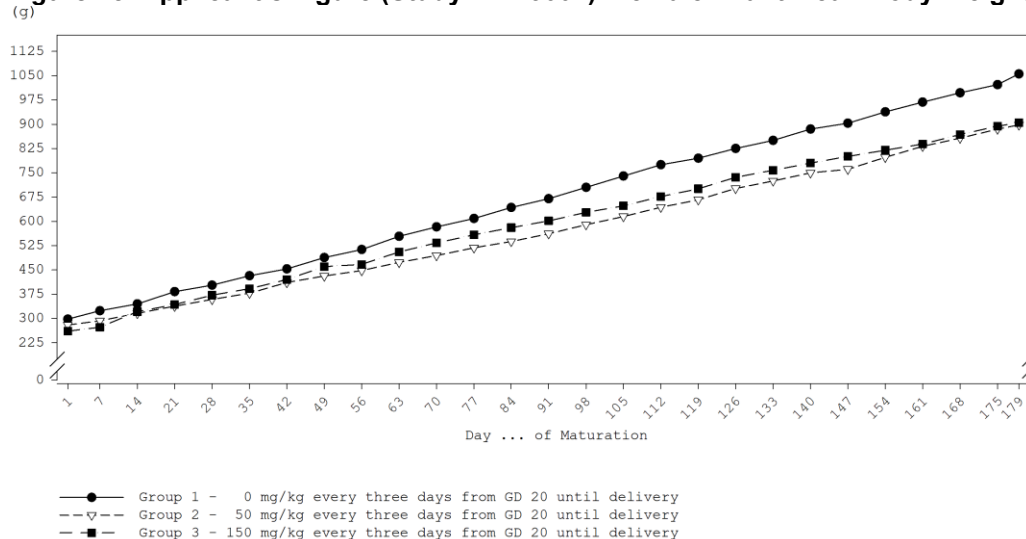
No test article-related effects were observed.

Birth Body Weights

- Infants with a birth body weight of less than 300 g in the C groups were: 2 premature births (prior to GD 140) and 2 early births (GDs 145 and 148) and 2 born at term.
- Infants with low body weights in the LD were: one premature birth (GD 139) one early birth (GD 145) and one at term (GD 157).
- Infants with low body weights in the HD were: two early births (GDs 133 and 144) that were found dead, and one early birth (GD 145) that remained at a very low weight at PND 7 and died on PND 11.
- Body weights from PND 7: Body weight and weight gains of surviving infant males were similar among groups. Body weight gains of surviving dosed female infants were less than controls.

Figure 15. Applicant's Figure (Study NCD3001): Male Infant Mean Body Weights

Source: Applicant's Figure (Study NCD3001)

Figure 16. Applicant's Figure (Study NCD3001): Female Infant Mean Body Weights

Source: Applicant's Figure (Study NCD3001)

Physical Development

Size correlated with body weights, but there were no test article effects on body measurements, grip strength, skeletal development, heart rates, or ophthalmologic exams.

Hematology

- Elevated platelet counts and giant platelets were reported in 3 HD and 2 C infants. Differences in other parameters were sporadic and lacked correlation to dose.

Clinical Chemistry

- No test article-related effects were reported.

Immunotoxicology

Immunophenotyping

- No test article-related effects were seen in relative or absolute numbers of CD3+ T cells, CD3+CD8+ cytotoxic T cells, CD3+CD4+ T helper-cells, CD20+ B-cells, or CD16+ natural killer cells.
- No test article-related effects were seen in splenic B cells, naïve B cells, germinal center B cells, plasma blasts, or total CD3+ T-cells, nor in bone marrow plasma cells, plasma blasts, or CD-3+ T cells.
- T Cell-Dependent Antibody Response
 - 1 mL keyhole limpet hemocyanin (KLH) was administered SC on PND 119 and again on PND 147. Samples were collected and analyzed from pre-dose PND 119 and 147, and 7-, 14-, and 21-days post-inoculation (on PNDs 126, 133, 140, 154, 161, 168, and 175).
- IgM anti-KLH titers were similar among groups and peaked 7-14 days after the first and second immunizations. All three groups developed IgG responses, and the titers uniformly peaked on day 154 - after the second immunization. Although male group sizes were similar (6 CM, 5 MDM, and 7 HDM infants), female group sizes varied (4 CF, 7 MDF, and 3 HDF infants) and there was notable inter-animal sampling variability in all groups. IgG titers in HDM infants were lower than in CM and MDM infants. IgG titers were reduced in MDF and HDF compared to CF infants.
- Maternal ADA had no apparent effect on the infant immune responses.

Neurological Assessment

- Results of examinations in male and female infants on PND 1 and 7, to include postural tonus, hip and shoulder abduction, knee, finger, and toe flexion, righting reflex, progression while prone, eye tracking, lip smacking, suckling, “snout reflex,” nystagmus, and Moro reflex, did not differ among groups. Grip strength, tested on PND 28, was similar among groups.
- ADA was detected in infants born to females that developed ADA. As seen in maternal females, the frequency and level of ADA was greater in infants in the mid dose group.

Toxicokinetics

- Drug was not detected in LD infants at any time. On day 1 at the HD, the mean infant concentration was 9.30 /ml; (compared to maternal levels of 584 ug/mL) and no drug was quantifiable by PND 7 and 28.
- Pathology findings in infants surviving through maturation

Necropsy

- On LD/PND 180 $\pm$ 1. Mothers and infants were necropsied together. Intramuscular ketamine was followed by IV barbiturates and then exsanguination. After body weights were determined, and a full macroscopic examination, organs were weighed. Tissues were preserved, processed, and examined histologically as described for the maternal necropsy procedures (above).
- Organ weights: No test article-related effects on organ weights were reported.
- No macroscopic or microscopic test article-related effects were seen.

14. Clinical Pharmacology

14.1. In Vitro Studies

Rozanolixizumab is a human IgG4 monoclonal antibody to target and bind to FcRn receptor with increased affinity. It is neither subject to CYP450 metabolism nor expected to interfere with cytokine levels. Further, rozanolixizumab 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

Study UP0018/UK: First-in-Human, Phase 1, Single-Ascending Dose Study in Healthy Volunteers

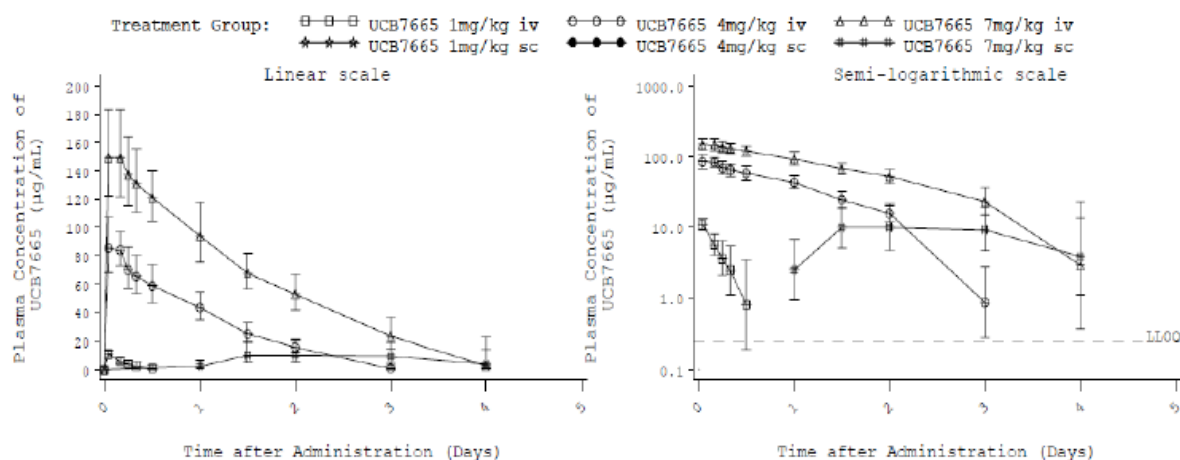
Study Design

UP0018 was a first-in-human, randomized, participant- and investigator-blind, placebo-controlled, single dose-escalating study conducted in healthy study subjects. Each study participant was randomized to 1 of 6 cohorts and received a single dose of placebo (n=2 per cohort) or rozanolixizumab at a dose of $\approx$ 1 mg/kg, $\approx$ 4 mg/kg, or $\approx$ 7 mg/kg (n=6 per cohort) administered intravenously (IV) or SC as a 1-hour infusion. The study objectives were to assess safety, tolerability, PK, PD, and immunogenicity.

A total of 49 subjects were randomized to 6 dosing cohorts and were included in the full analysis set and the pharmacodynamic per-protocol set. Additionally, all 36 subjects who received rozanolixizumab were included in the pharmacokinetic per-protocol set.

The plasma concentration-time profiles for rozanolixizumab administered by the IV route showed similar profiles for the $\approx$ 4 mg/kg and $\approx$ 7 mg/kg doses, with nonlinear increases in rozanolixizumab plasma concentrations consistent with target-mediated disposition. Rozanolixizumab administered by the SC route was detectable only at the highest concentration of $\approx$ 7 mg/kg. There was no effect of ADA on the plasma concentrations of rozanolixizumab.

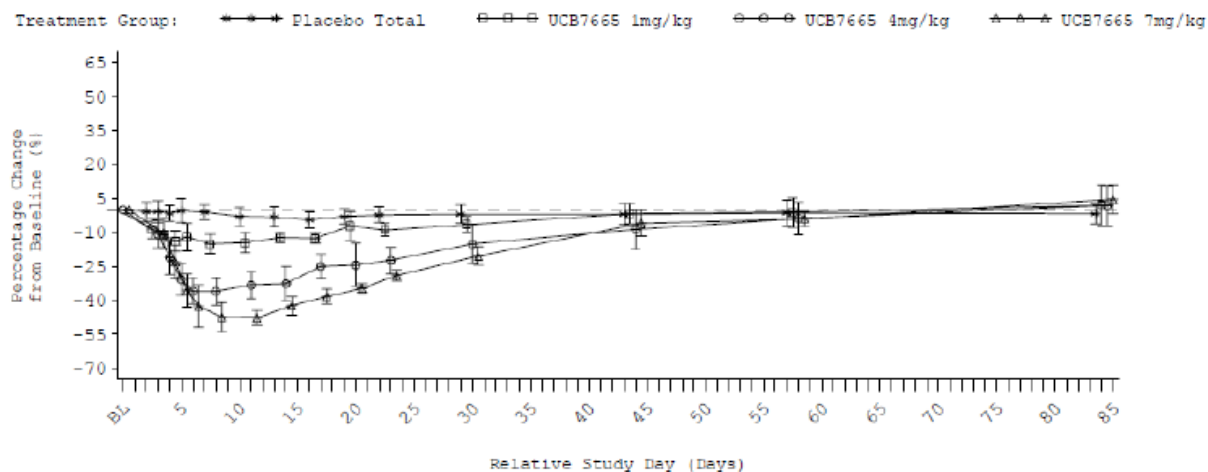
Figure 17. Geometric Mean (With 95% CIs) Rozanolixizumab Plasma Concentration-Time Profile: IV and SC Comparison



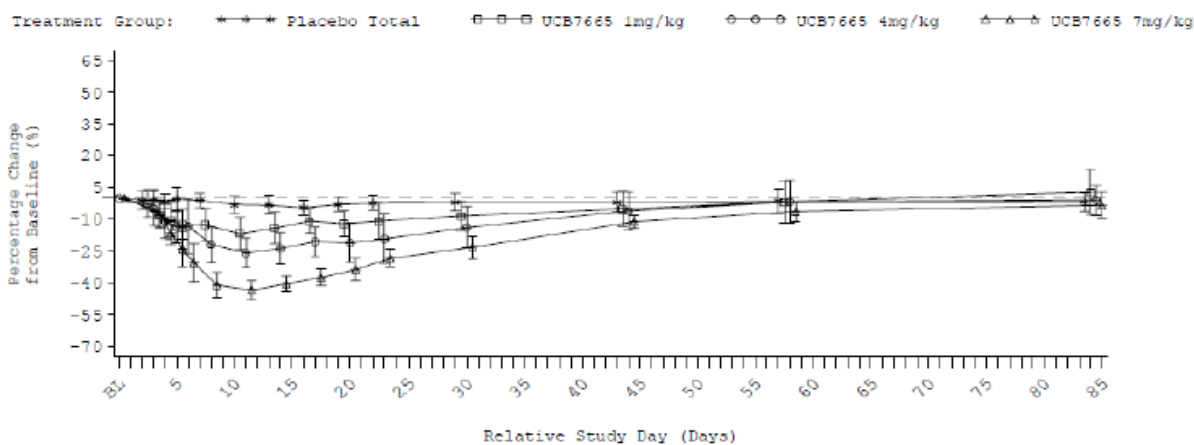
Source: Clinical Study Report for UP0018

Figure 18. Mean Percentage Change From Baseline in Total IgG Over Time

Variable: Immunoglobulin G - TDL (g/L)
Route of Administration: iv



Variable: Immunoglobulin G - TDL (g/L)
Route of Administration: sc



Source: Clinical Study Report for UP0018.

14.3. Bioanalytical Method Validation and Performance

Quantification of rozanolixizumab in plasma was performed using electrochemiluminescence assay on the Meso Scale Discovery platform. For phase 1 Study UP0018 and phase 2 Study (MG0002), a sandwich format using an anti-idiotypic rozanolixizumab rabbit monoclonal antibody as capture and a goat antihuman Kappa light chain antibody for detection was used (PK-1). This method was redeveloped as a sandwich format using an anti-idiotypic rozanolixizumab rabbit monoclonal antibody as capture and for detection to increase assay sensitivity, dynamic range, adopt newly labeled reagents, and validate according to the latest guidance (PK-2) for phase 1 Study UP0060 and phase 3 Study MG0003.

The method validation parameters and performance characteristics are summarized as PK method 1 and PK method 2 in tables below.

Table 75 Method Performance for Determination of Rozanolixizumab in Plasma – PK Method 1

	UCB7665	
Validated Range	2.50 to 100 ng/mL*	
Calibration Curve Fit	4 parameter with $1/Y^2$ weighting	
Minimum required dilution	100-fold in Assay Diluent	
Linearity of dilution	30,000-fold	
Assay range	250 to 3000000 ng/mL**	
Precision (%CV) Intra-assay	≤15.8%	
Precision (%CV) Inter-assay	VC1 ≤ 25 % VC2 to VC4 ≤ 20 % VC5: 34 %	
Accuracy (%RE) Intra-assay	VC1 to VC5 : -16.3 to 19.2 %RE	
Accuracy (%RE) Inter-assay	-17.2 to 7.6%	
Selectivity	Spike A (2500ng/mL)	Spike B (200ng/mL)
	-8.9 to 18.5 %RE from 10 individuals (10/10 acceptable) Haemolysed sample: Acceptable Lipidaemic sample: Acceptable	-17.1 to 23.5 %RE from 10 individuals (9/10 acceptable) Haemolysed sample: Acceptable Lipidaemic sample: Acceptable
Stability of UCB7665 Excipient Buffer	208 days at nom -80°C	
Stability of UCB7665 in plasma after storage at room temperature	-3.5 to 15.5 %RE after 24 hours at nom' 22°C	
Stability of UCB7665 in plasma after 5 cycles freeze-thaw	-6.6 to 4.5 %RE	
Stability of UCB7665 in plasma after long term storage	≤±20% RE after 101 days at nom' -80°C	
Hook Effect	Not evident up to 10,000 ng/mL	
Drift	Not evident	

Source: Validation report of PK method 1 (b) (4) 267108qb02-up0018rep.pdf), page 9 of 109

Table 76 Method Performance for Determination of Rozanolixizumab in Plasma – PK Method 2

Overview	
Short description of the method	Manual Immunoassay
Biological matrix	Huma plasma (Li Hep)
Analyte	UCB7665
Calibration model:	
Fit	4PL (auto estimate)
Weighting	1/Y ²
Assay calibration range	200 to 12800 ng/mL (in whole matrix)
Sample volume	50 µL
Upper limit of quantitation	12800 ng/mL (Calibration Standard S1; -5.5 % RE; 6.3% CV)
Lower limit of quantitation	200 ng/mL (Calibration Standard S7; 1.5% RE; 1.6% CV)
Dilution	
Maximum dilution factor	1000-fold (in human serum prior to MRD).
MRD in assay diluent	100-fold.
Full quantitation range in whole matrix equivalent (WME)	200 to 12800 ng/mL
QC theoretical concentrations (ng/mL)	LLQC: 200 LQC: 600 MQC: 1600 HQC: 9600 ULQC: 12800 VHQC: :50000
Precision and Accuracy	
Intra-batch accuracy (% RE) (each individual P&A batch)	LLQC: -13.7 to 7.4% RE LQC: -4.8 to 12.1% RE MQC: 0.0 to 12.5% RE HQC: 6.3 to 14.6% RE ULQC: 0.8 to 11.7% RE
Intra-batch precision (% CV) (each individual P and A batch)	LLQC: ≤ 2.9% CV LQC: ≤ 4.0% CV MQC: ≤ 4.0% CV HQC: ≤ 6.1% CV ULQC: ≤ 10.6% CV
Inter-batch accuracy (Av %RE) (all P and A batches)	The maximum Av RE% was 10.4%.
Inter-batch precision (Av %CV) (all P and A batches)	The maximum Av CV% was 7.9%.
Inter-batch total error (Av %TE) (all P and A batches)	The maximum Av TE% was 15.3%.

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Rystiggo (rozanolixizumab)

ANOVA:	
Intra-batch precision (Max)	6.37% for the ULQC
Inter-batch precision (Max)	4.78% for the LQC
Inter-analyst precision (Max)	8.79% for the LLQC.
Inter-batch accuracy (Max)	10.43% for the HQC.
Inter-batch Total Error (Max)	12.94% for the HQC.
Selectivity	
	Confirmed for UCB7665 in ten independent control blank healthy human plasma samples.
In 10 individuals and pooled plasma	Successfully demonstrated at LLOQ (10/10 individuals plus pool) and high spiked concentration (9600 ng/mL, 9/10 individuals plus pool).
Specificity	
Specificity of UCB7665 in the presence of FcRn (%RE)	Specific for UCB7665 at the LLOQ up to 10 ng/mL of FcRn.
	Interference was seen at 50, 100 and 200 ng/mL at the LLOQ for UCB7665.
	Specific for UCB7665 at the ULOQ up to 200 ng/mL of FcRn.
Stability	
Sample stability in human plasma	Confirmed up to 24 hours at RT
Freeze thaw stability	10 cycles at nominally -80°C
Long term stability in human plasma	Confirmed up to 30 days at nominally -80°C
Stability of the working stock solution	Confirmed up to 46 days at nominally -80°C storage
Hook effect (Prozone)	
Findings	The method is not susceptible to hook effect up to 2mg/mL of UCB7665
Drift:	
Findings	No evidence of drift
Drug Bridging (QCs prepared from new UCB7665 batch):	
Intra-batch accuracy (% RE)	LLQC: -7.0 to -3.3 % RE LQC: -7.8 to -4.7 % RE MQC: -11.9 to -9.4% RE HQC: -16.1 to -1.7% RE ULQC: -22.8 to 2.3% RE
Intra-batch precision (% CV)	LLQC: ≤ 3.3% CV LQC: ≤ 1.5% CV MQC: ≤ 2.0% CV HQC: ≤ 16.4% CV ULQC: ≤ 22.6% CV

Intra-batch precision (% TE)

LLQC: ≤ 9.4% TE
LQC: ≤ 8.3% TE
MQC: ≤ 12.9% TE
HQC: ≤ 25.3% TE
ULQC: ≤ 29.6% TE

Source: Validation report of PK method 2 (NCD3097.pdf), pp. 12–14 of 155

Reviewer's Comments: *The reviewer agrees that the bioanalytical method validation and performance is adequate for quantification of plasma rozanolixizumab concentrations in Studies UP0018, UP0060, MG0002 and MG0003 and are in accordance with the criteria outlined in the FDA bioanalytical guidance.*

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

Summary of Clinical Studies

Immunogenicity of rozanolixizumab was evaluated in two phase 1 Studies (UP0018 and UP0060, healthy subjects), four phase 2 Studies (MG0002, TP0001, CIDP01, and CIDP04), and three phase 3 Studies (MG0003, MG0004, and MG0007). Subjects completed Study MG0003 were eligible to continue receiving rozanolixizumab treatment in the open-label extension (OLE) Study MG0007. Studies MG0003 and MG0007 provided main data for IS analysis to assess the impact of immunogenicity on PK. Study MG0004 is not evaluated since approximately half of the study subjects had fewer than 18 weeks of exposure and rolled over to Study MG0007 upon site initiation.

The subsequent analysis presented in this section is considered exploratory because there are limitations due to analytical assay sensitivity.

[Table 77](#) contains (1) the information for key individual studies assessing immunogenicity and (2) a high-level summary of study results for PK (trough concentration). Overall study design in terms of treatment duration, sampling time, and sample size were adequate to assess the ADA impact on PK.

Table 77. Summary of Clinical Studies Information and Incidence Rates for Immunogenicity

Clinical Information Category	Clinical Study Information			
Studies	MG0003		MG0007 (OLE to MG0003)	
Dose	≈7 mg/kg, ≈10 mg/kg		≈7 mg/kg, ≈10 mg/kg	
Dosing frequency	Weekly		Weekly	
Treatment duration	6 weeks (1 cycle)		Repeated 6-week cycles	
Status	OP: 8 weeks		based on symptom worsening	
Number subject who received rozanolixizumab	Completed		OP: 16-22 weeks	
Applicant reported ADA incidence	133		Ongoing ^a	
Applicant reported NAb incidence	37.2% (48/129)		165	
FDA calculated ADA incidence	20.2% (26/129)		46.3% (69/149)	
FDA calculated NAb incidence (among ADA+)	37% (49/133)		32.2% (48/149)	
	57% (28/49)		44.4% (71/160)	
Dose	≈7 mg/kg	≈10 mg/kg	≈7 mg/kg	≈10 mg/kg
Applicant reported rozanolixizumab trough concentration at cycle 1 day 43 (μg/mL)	0.1 ^b	0.1	0.1	0.1

Source, CSR MG0003 page number 163 and MG0007 page number 173

a) Interim immunogenicity data (submission data cut-off date: 08 Jul 2022) from the ongoing phase 3 OLE study in gMG (generalized Myasthenia Gravis)

b) 0.1 represent BLQ since the Applicant used LLOQ/2 for sample with BLQ concentration

Abbreviations: NAb, neutralizing antibody; OLE, open-label extension; OP: observation period

Highlight of Key Characteristics of Immunogenicity Assays Relevant to This Review

The ADA assay has adequate sensitivity and drug tolerance. [Table 78](#) shows several assay characteristics that are relevant for the analysis.

Table 78. Summary of Key Assay Characteristics Related to Immunogenicity Assessment

Studies	MG0003, MG0007
Assay validation report number (ADA)	ADA Assay: NCD3256
ADA assay sensitivity	7.66 ng/mL
ADA assay drug tolerance	The assay can detect 100 ng/mL of ADA positive control in the presence of 200 μg/mL rozanolixizumab.

Source: UCB Study Number: NCD3256 page number 44

Abbreviations: ADA, assay validation report number

Methods for Evaluating the Effect of Immunogenicity on PK of Rozanolixizumab

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in two groups (ADA+ and ADA-) in subjects with time-matched PK and ADA data using Immunogenicity Specimen (IS) tool developed in-house. At each timepoint, rozanolixizumab concentrations are summarized by ADA+ and ADA- groups. Summary of rozanolixizumab concentrations by ADA status (ADA+ or ADA-) are tabulated along with the geometric mean (GM) concentration by timepoint as well as the number of subjects. For the statistical comparisons of concentration data between ADA+ and ADA- groups, the geometric mean ratio (GMR) of ADA+/ADA- and the corresponding 90% CI are tabulated.

Data from MG0003 (completed study) and MG0007 (interim data) were analyzed and summarized by dose groups (≈7 mg/kg and ≈10 mg/kg) below.

Effect of Immunogenicity on PK of Rozanolixizumab – Results

Analysis results for Studies MG0003 and MG0007 indicate that the development of ADA in Study MG0007 is associated with a reduced systemic concentration of rozanolixizumab, and the effect of ADA is visible at several timepoint.

Study MG0003 – (Subjects Received ≈ 7 mg/kg or ≈ 10 mg/kg Rozanolixizumab Dose)

For the subjects in dose group received ≈ 7 mg/kg, the ADA+ group has a lower rozanolixizumab concentration than ADA- group at day 15, indicating that ADA has a negative effect on PK of rozanolixizumab. However, during the 43 days of treatment the GMR values were around 1 for the remaining timepoints and the 90% CI contained 1 at all timepoints. See [Table 79](#), below for summary of rozanolixizumab concentrations (geometric mean values) in Study MG0003 in ADA+ and ADA- subjects during the treatment period (43 days).

For the subjects in dose group received ≈ 10 mg/kg, as shown in [Table 80](#), the number of subjects in ADA+ groups are limited to accurately calculate the GMR and 90% CI except for on day 43 where the GMR was >1 and the 90% CI contains 1.

Table 79. Study MG0003(≈ 7 mg/kg) – Summary of Geometric Mean Concentration by ADA Status by Sample Analysis at Each Study Visit

Visit #	Treatment Day	Total N	Rozanolixizumab Geometric Mean Concentration ($\mu\text{g/mL}$)				GMR (90%CI) ADA+/ADA-
			ADA+ Group	N	ADA- Group	N	
2	Day 15	57	0.10	6	0.13	51	0.79 (0.4,1.6)
3	Day 24	12	12.50	1	12.05	11	1.03 (NA)
4	Day 29	20	0.10	4	0.11	16	0.90 (0.5,1.4)
5	Day 43	60	0.13	16	0.10	44	1.30 (1.1,1.5)

Source: FDA analysis

*90%CI not reported for timepoints with one subject in the ADA+ group

Abbreviations: ADA, assay validation report number; GMR: geometric mean ratio; N, number of subjects

Table 80. Study MG0003 (≈ 10 mg/kg Group) – Summary of Geometric Mean Concentration by ADA Status at Each Study Visit

Visit #	Treatment Day	Total N	Rozanolixizumab Geometric Mean Concentration ($\mu\text{g/mL}$)				GMR (90%CI) ADA+/ADA-
			ADA+ Group	N	ADA- Group	N	
2	Day 15	61	0.10	2	0.34	59	0.3 (0.1,1.2)
3	Day 24	24	2.24	2	8.31	22	0.3 (0,7.6)
4	Day 29	17	0.10	1	0.50	16	0.20 (NA)
5	Day 43	64	0.41	8	0.40	56	1.10 (0.3,3.9)

Source: FDA analysis

*90%CI not reported for time points with one subject in the ADA+ group

Abbreviations: ADA, assay validation report number; GMR, geometric mean ratio; N, number of subjects

Study MG0007 (Subjects Received ≈ 7 mg/kg or ≈ 10 mg/kg Rozanolixizumab Dose)

For the subjects in dose group received ≈ 7 mg/kg, upon receiving five 6-week dosing cycles, at a mean-level, ADA+ group was up to a 40% lower rozanolixizumab concentration than ADA- group ([Table 81](#)), indicating that ADA has a negative effect on PK of rozanolixizumab. See [Table 82](#) for a tabular summary of rozanolixizumab geometric mean concentration in Study MG0007 (≈ 10 mg/kg) during the treatment period in ADA+ subjects in whom there was up to 60% lower rozanolixizumab concentration than ADA- group.

Table 81. Study MG0007 (≈ 7 mg/kg Group) – Summary of Geometric Mean Concentration by ADA Status at Each Study Visit

Visit #	Treatment Day	Total N	Rozanolixizumab Geometric Mean Concentration ($\mu\text{g/ml}$)				GMR (90%CI) ADA+/ADA-
			ADA+ Group	N	ADA-Group	N	
2	Cycle 1/day 1	64	0.11	19	0.10	45	1.11 (0.9,1.3)
3	Cycle 1/day 22	46	0.15	11	0.14	35	1.10 (0.6,2.0)
4	Cycle 1/day 43	75	0.10	26	0.18	49	0.56 (0.4,0.9)
5	Cycle 2/day 43	48	0.15	20	0.17	28	0.92 (0.5,1.8)
6	Cycle 3/day 43	32	0.13	14	0.16	18	0.80 (0.4,1.6)
7	Cycle 4/day 43	18	0.29	11	0.24	7	1.20 (0.3,5.2)
8	Cycle 5/day 1	11	0.10	6	0.22	5	0.45 (0.1,1.7)
9	Cycle 5/day 43	9	0.10	5	0.17	4	0.60 (0.4,1.0)

Source: FDA analysis

Abbreviations: ADA, assay validation report number; GMR, geometric mean ratio; N, number of subjects

Table 82. Study MG0007 (≈ 10 mg/kg Group) – Summary of Geometric Concentration by ADA Status at Each Study Visit

Visit #	Treatment Day	Total N	Rozanolixizumab Geometric Mean Concentration ($\mu\text{g/mL}$)				GMR (90%CI) ADA+/ADA-
			ADA+ group	N	ADA- group	N	
2	Cycle 1/day 22	47	0.24	13	0.45	34	0.53 (0.2,1.6)
3	Cycle 1/day 43	63	0.11	14	0.30	49	0.38 (0.2, 0.9)
4	Cycle 2/day 1	48	0.10	11	0.11	37	0.89 (0.6,1.3)
5	Cycle 2/day 43	43	0.35	10	0.36	33	0.97 (0.3,3.2)
6	Cycle 3/day 43	26	0.36	7	0.32	19	1.10 (0.2,4.9)
7	Cycle 4/day 43	12	0.10	3	0.24	9	0.42 (0.1,2.7)
8	Cycle 5/day 43	4	0.10	3	0.38	1	0.26 (NA)

Source: FDA analysis

*90%CI not reported for time points with one subject in the ADA+ group

Abbreviations: ADA, assay validation report number; GMR, geometric mean ratio; N, number of subjects

Effect of Immunogenicity on Efficacy/Safety of Rozanolixizumab

As per the Applicant, there was no clinically meaningful impact of ADA (including neutralizing ADA) on efficacy (MG-ADL) (see [Table 83](#) below for reference). Additionally, the Applicant noted that presence of higher ADA or NAb titer did not have a clear effect on individual changes from baseline in MG-ADL score (see [Figure 19](#) and [Figure 20](#) below for reference).

The reviewer analysis confirmed the Applicant's findings. The impact of ADA positivity on the total IgG profile was evaluated in the phase 3 Studies where occurrence of ADA on changes in MG-ADL score (for efficacy) or changes in pain, diarrhea, injection site reactions, and headache (for safety) were not significantly different.

Table 83 Impact of ADA (Including Neutralizing ADA) on PD (Total IgG Reduction) and Efficacy (MG-ADL)

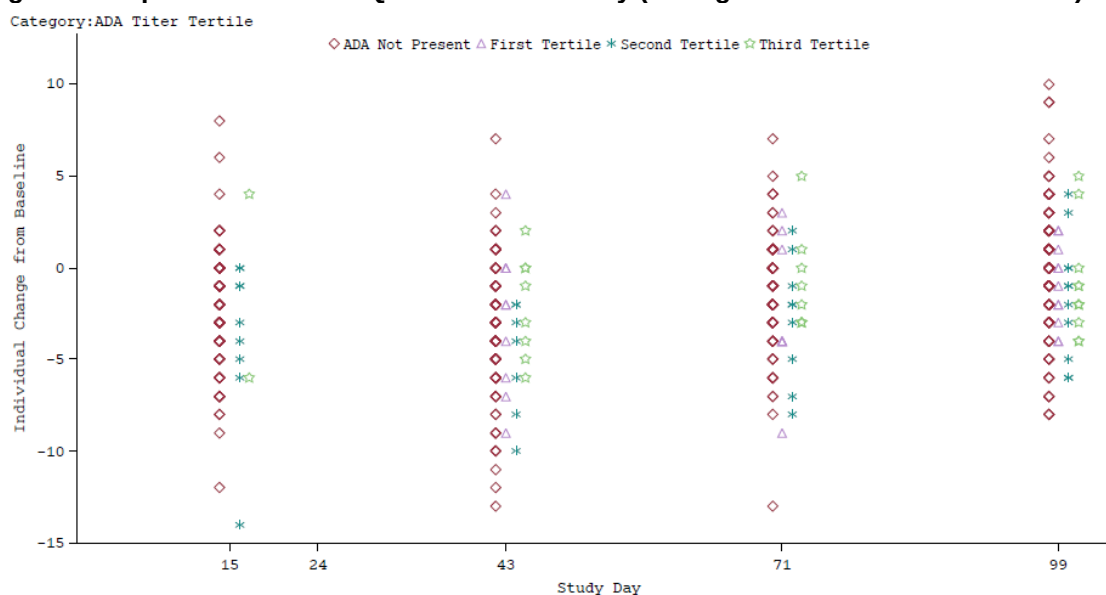
ADA Categorization by Day: 43

Treatment Group	ADA Participant Category	N	Total IgG	MG-ADL
			Mean Maximum % Change from Baseline up to Day 43	Mean Change from Baseline at Day 43
RLZ ~7mg/kg	ADA-NEG [1]	40	-72.74	-3.68
	Inconclusive [2]	0		
	TE-POS, NAb-POS [3]	10	-63.94	-2.90
	TE-POS, NAb-NEG [4]	10	-77.90	-2.80
	Non-TE-POS, NAb-POS [5]	0		
	Non-TE-POS, NAb-NEG [6]	0		
RLZ ~10mg/kg	ADA-NEG [1]	47	-78.61	-3.11
	Inconclusive [2]	0		
	TE-POS, NAb-POS [3]	3	-74.06	-4.33
	TE-POS, NAb-NEG [4]	13	-78.30	-3.46
	Non-TE-POS, NAb-POS [5]	0		
	Non-TE-POS, NAb-NEG [6]	1	-92.03	-4.00

Refer to footnotes on the last page.

Source: Integrated Summary of Immunogenicity

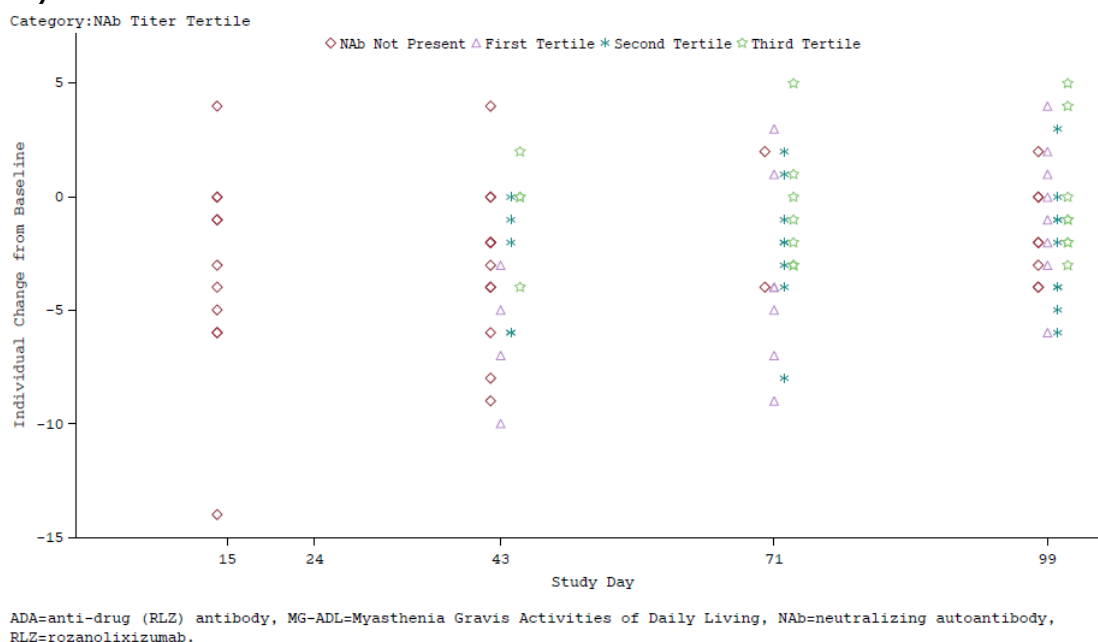
Figure 19 Impact of ADA Titer Quartiles on Efficacy (Change from Baseline in MG-ADL)



ADA=anti-drug (RLZ) antibody, MG-ADL=Myasthenia Gravis Activities of Daily Living, NAb=neutralizing autoantibody, RLZ=rozanolixizumab.

Source: Integrated Summary of Immunogenicity.

Figure 20 Impact of Neutralizing ADA Titer Quartiles on Efficacy (Change from Baseline in MG-ADL)



Source: Integrated Summary of Immunogenicity.

14.5. Pharmacometrics Assessment

14.5.1. Applicant's Analysis

The population analyses were conducted using plasma concentrations of rozanolixizumab and total serum IgG concentrations in studies UP0106, UP0018, UP0060, TP0001, MG0002, MG0003, and MG0004; serum concentrations of anti-AChR and anti-MuSK from Studies MG0002, MG0003, and MG0004; and MG-ADL score data from MG0003. Interim data from MG0007 was used for external validation of the PK and total IgG models, and MG-ADL data from MG0002 for external validation of the MG-ADL model.

Data used in the popPK/PD analysis and a brief description of these studies is given in [Table 84](#).

Model development was based on 898 rozanolixizumab plasma concentrations from 266 subjects (65 healthy volunteers, 154 gMG patients, and 47 ITP patients), 5,566 total IgG levels from 412 subjects (103 healthy volunteers, 243 gMG patients, and 66 ITP patients), 1,202 anti-AChR observations from 203 gMG patients, 116 anti-MuSK observations from 17 gMG patients, and 2,180 MG-ADL scores from 200 gMG patients.

Table 84. Summary of the Characteristics of the Studies Used for PopPK/PD Analyses

Protocol/Title	Subject Population	No. of Subjects	Dose (SC)	No. of PK Samples Included in Analysis Dataset	No. of BLQ Samples Excluded from Analysis Dataset
UP0018 phase 1, Randomized, Double-blind, Placebo- controlled Study	Healthy Subjects	0	Placebo	0	14
		0	≈1 mg/kg	0	72
		2	≈4 mg/kg	6	66
		6	≈7 mg/kg	34	49
		8	All	40	201
UP0060 phase 1, Multicenter, Randomized, Double-blind, Placebo-controlled Study	Healthy subjects	0	Placebo	0	6
		6	≈4 mg/kg	23	81
		1	≈6 mg/kg	9	4
		19	≈7 mg/kg	133	114
		20	≈10 mg/kg	144	116
		46	All	309	321
UP0106 phase 1, Randomized, Double-blind, Placebo- controlled Study	Healthy subjects	11	≈560 mg	74	89
MG0002 phase 2, Randomized, Double-blind, Placebo- controlled Study	gMG patients	0	Placebo	0	169
		1	≈4 mg/kg	3	120
		15	≈7 mg/kg	28	247
		16	All	31	536
TP0001 phase 3, Randomized, Double blind, Placebo-controlled Study	ITP patients	5	≈4 mg/kg	8	104
		0	≈6 mg/kg	0	3
		8	≈7 mg/kg	15	72
		0	≈9 mg/kg	0	3
		11	≈10 mg/kg	24	33
		11	≈15 mg/kg	17	21
		12	≈20 mg/kg	33	14
		47	All	97	250
MG0003 phase 3, Randomized, Open-label Study	gMG patients	0	Placebo	0	4
		63	≈7 mg/kg	122	264
		69	≈10 mg/kg	193	203
		130	All	315	471
MG0004 phase 3, Randomized, Open-label Study	gMG patients	13	≈7 mg/kg	16	113
		12	≈10 mg/kg	16	77
		23	All	32	190

Source: Adapted from the Applicant's popPK report c 0534 pp. 21–24, Table 1 and Response to IR dated 17 May 2013 pp 2–3, Table 1

Subjects who received more than one dose level in a study were counted for each dose level. Subjects who participated in more than one study are counted for the totals in each study but are counted only once for the overall total ('All'), e.g., 200 subjects from Study MG0003 are included in the IgG analysis data set; 68 of those subjects also participated in Study MG0004. The doses for MG0003 and MG0004 are weight-tiered approximating 7 mg/kg and 10 mg/kg. The 6 mg/kg dose in UP0060 and the 6 mg/kg and 9 mg/kg doses in TP0001 were due to a lower than planned administered dose. The lower limit of quantification for each study is listed in the data definition table in CL0534 Report Appendix 4.

Abbreviations: BLQ, below limit of quantification; gMG, generalized myasthenia gravis; ITP, immune thrombocytopenia; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population pharmacokinetics; SC, subcutaneous

Listings of the baseline demographics for the continuous and categorical variables for these subjects are given in [Table 85](#) and [Table 86](#), respectively.

Table 85. Baseline Continuous Covariate Statistics in the Analysis Data Sets, Stratified by Study

	UP0018 N=24	UP0060 N=65	MG0002 N=43	TP0001 N=66	MG0003 N=200	UP0106 N=14	Overall N=412
Age (years)							
Mean (SD)	46.6 (13.6)	36.5 (10.8)	51.9 (15.1)	50.8 (17.4)	51.8 (16.3)	37.5 (11.3)	48.5 (16.3)
Median (min, max)	49.0 (23.0, 65.0)	34.0 (20.0, 60.0)	51.0 (25.0, 81.0)	54.0 (20.0, 86.0)	52.0 (18.0, 89.0)	37.5 (22.0, 61.0)	48.0 (18.0, 89.0)
Body weight (kg)							
Mean (SD)	77.9 (11.1)	66.5 (13.2)	87.1 (20.5)	76.8 (15.1)	81.1 (23.9)	61.8 (15.7)	77.9 (21.0)
Median (min, max)	77.4 (58.6, 98.6)	64.0 (46.2, 94.2)	88.0 (42.5, 136)	75.2 (51.4, 122)	78.0 (37.7, 156)	59.1 (45.0, 97.6)	76.0 (37.7, 156)
Height (cm)							
Mean (SD)	175 (9.47)	168 (8.98)	167 (9.28)	167 (8.52)	170 (9.85)	164 (9.71)	169 (9.62)
Median (min, max)	174 (158, 193)	168 (150, 183)	168 (147, 188)	165 (151, 184)	170 (149, 198)	162 (153, 186)	168 (147, 198)
Body mass index (kg/m²)							
Mean (SD)	25.4 (3.23)	23.4 (3.10)	31.3 (7.66)	27.5 (4.85)	27.8 (6.43)	22.7 (3.12)	27.1 (6.10)
Median (min, max)	25.7 (19.5, 29.8)	23.4 (18.6, 31.2)	30.5 (18.4, 47.1)	27.6 (18.2, 42.0)	27.2 (13.7, 47.6)	21.9 (18.7, 28.2)	26.4 (13.7, 47.6)
eGFR (ml/min/1.73²)							
Mean (SD)	94.0 (15.4)	111 (16.3)	93.5 (17.9)	98.6 (23.8)	97.8 (19.2)	112 (14.5)	99.8 (19.9)
Median (min, max)	97.6 (61.6, 120)	113 (70.7, 140)	95.7 (38.2, 122)	99.6 (38.9, 161)	99.8 (47.0, 142)	113 (85.2, 133)	101 (38.2, 161)
ALT (U/L)							
Mean (SD)	28.2 (11.5)	20.0 (10.2)	21.7 (14.7)	25.3 (11.6)	22.5 (18.5)	21.2 (8.51)	22.8 (15.5)
Median (min, max)	25.0 (11.0, 59.0)	18.0 (8.00, 64.0)	16.0 (8.00, 86.0)	22.5 (8.00, 69.0)	18.0 (3.00, 158)	19.5 (11.0, 39.0)	19.0 (3.00, 158)
AST (U/L)							
Mean (SD)	21.5 (4.04)	22.8 (5.23)	21.8 (8.14)	23.0 (5.92)	20.9 (12.2)	21.6 (3.50)	21.7 (9.50)
Median (min, max)	20.5 (16.0, 31.0)	22.0 (13.0, 38.0)	21.0 (10.0, 50.0)	22.0 (15.0, 40.0)	18.0 (9.00, 127)	22.0 (15.0, 27.0)	20.0 (9.00, 127)
ALP (U/L)							
Mean (SD)	72.5 (20.0)	50.9 (14.1)	74.1 (24.0)	71.0 (33.8)	63.2 (31.0)	45.9 (12.6)	63.6 (28.7)
Median (min, max)	72.5 (43.0, 114)	49.0 (33.0, 98.0)	73.0 (43.0, 140)	65.0 (27.0, 245)	59.0 (22.0, 386)	48.0 (28.0, 68.0)	58.0 (22.0, 386)
Bilirubin (μmol/L)							
Mean (SD)	9.83 (3.81)	14.0 (5.50)	10.7 (6.05)	11.5 (5.66)	11.2 (5.58)	11.6 (2.75)	11.6 (5.56)
Median (min, max)	9.00 (5.00, 18.0)	12.8 (4.70, 29.6)	9.30 (4.20, 30.7)	10.4 (4.40, 32.7)	10.4 (3.50, 37.2)	11.4 (7.50, 19.5)	10.8 (3.50, 37.2)

Since subjects included in Study MG0004 (68 subjects) were also included in study MG0003, they are removed from this table, for correct calculation of summary statistics.

Overall presents the statistics for all unique subjects.

Source: The Applicant's popPK report cl0534 Page 32, Table 6

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate

Table 86. Baseline Categorical Covariate Statistics in the Analysis Data Sets, Stratified by Study

	UP0018 N=24	UP0060 N=65	MG0002 N=43	TP0001 N=66	MG0003 N=200	UP0106 N=14	Overall N=412
Age (years)							
Mean (SD)	46.6 (13.6)	36.5 (10.8)	51.9 (15.1)	50.8 (17.4)	51.8 (16.3)	37.5 (11.3)	48.5 (16.3)
Median (min, max)	49.0 (23.0, 65.0)	34.0 (20.0, 60.0)	51.0 (25.0, 81.0)	54.0 (20.0, 86.0)	52.0 (18.0, 89.0)	37.5 (22.0, 61.0)	48.0 (18.0, 89.0)
Body weight (kg)							
Mean (SD)	77.9 (11.1)	66.5 (13.2)	87.1 (20.5)	76.8 (15.1)	81.1 (23.9)	61.8 (15.7)	77.9 (21.0)
Median (min, max)	77.4 (58.6, 98.6)	64.0 (46.2, 94.2)	88.0 (42.5, 136)	75.2 (51.4, 122)	78.0 (37.7, 156)	59.1 (45.0, 97.6)	76.0 (37.7, 156)
Height (cm)							
Mean (SD)	175 (9.47)	168 (8.98)	167 (9.28)	167 (8.52)	170 (9.85)	164 (9.71)	169 (9.62)
Median (min, max)	174 (158, 193)	168 (150, 183)	168 (147, 188)	165 (151, 184)	170 (149, 198)	162 (153, 186)	168 (147, 198)
Body mass index (kg/m²)							
Mean (SD)	25.4 (3.23)	23.4 (3.10)	31.3 (7.66)	27.5 (4.85)	27.8 (6.43)	22.7 (3.12)	27.1 (6.10)
Median (min, max)	25.7 (19.5, 29.8)	23.4 (18.6, 31.2)	30.5 (18.4, 47.1)	27.6 (18.2, 42.0)	27.2 (13.7, 47.6)	21.9 (18.7, 28.2)	26.4 (13.7, 47.6)
eGFR (ml/min/1.73²)							
Mean (SD)	94.0 (15.4)	111 (16.3)	93.5 (17.9)	98.6 (23.8)	97.8 (19.2)	112 (14.5)	99.8 (19.9)
Median (min, max)	97.6 (61.6, 120)	113 (70.7, 140)	95.7 (38.2, 122)	99.6 (38.9, 161)	99.8 (47.0, 142)	113 (85.2, 133)	101 (38.2, 161)
ALT (U/L)							
Mean (SD)	28.2 (11.5)	20.0 (10.2)	21.7 (14.7)	25.3 (11.6)	22.5 (18.5)	21.2 (8.51)	22.8 (15.5)
Median (min, max)	25.0 (11.0, 59.0)	18.0 (8.00, 64.0)	16.0 (8.00, 86.0)	22.5 (8.00, 69.0)	18.0 (3.00, 158)	19.5 (11.0, 39.0)	19.0 (3.00, 158)
AST (U/L)							
Mean (SD)	21.5 (4.04)	22.8 (5.23)	21.8 (8.14)	23.0 (5.92)	20.9 (12.2)	21.6 (3.50)	21.7 (9.50)
Median (min, max)	20.5 (16.0, 31.0)	22.0 (13.0, 38.0)	21.0 (10.0, 50.0)	22.0 (15.0, 40.0)	18.0 (9.00, 127)	22.0 (15.0, 27.0)	20.0 (9.00, 127)
ALP (U/L)							
Mean (SD)	72.5 (20.0)	50.9 (14.1)	74.1 (24.0)	71.0 (33.8)	63.2 (31.0)	45.9 (12.6)	63.6 (28.7)
Median (min, max)	72.5 (43.0, 114)	49.0 (33.0, 98.0)	73.0 (43.0, 140)	65.0 (27.0, 245)	59.0 (22.0, 386)	48.0 (28.0, 68.0)	58.0 (22.0, 386)
Bilirubin (μmol/L)							
Mean (SD)	9.83 (3.81)	14.0 (5.50)	10.7 (6.05)	11.5 (5.66)	11.2 (5.58)	11.6 (2.75)	11.6 (5.56)
Median (min, max)	9.00 (5.00, 18.0)	12.8 (4.70, 29.6)	9.30 (4.20, 30.7)	10.4 (4.40, 32.7)	10.4 (3.50, 37.2)	11.4 (7.50, 19.5)	10.8 (3.50, 37.2)

Since subjects included in Study MG0004 (68 subjects) were also included in study MG0003, they are removed from this table, for correct calculation of summary statistics.

Overall presents the statistics for all unique subjects.

Source: The Applicant's popPK report cl0534 Page 33, Table 7

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate

Pharmacokinetic (PK)/Immunoglobulin G (IgG) Modeling

A nonlinear mixed effects modelling approach was used, using nonlinear mixed-effects modeling (NONMEM) V7.4.4. Parameter estimation was performed using the first-order conditional estimation with interaction method. The structural population pharmacokinetics (popPK) model consisted of a one-compartment model with target-mediated drug disposition (TMDD) using the quasi-equilibrium approximation. This implies two elimination pathways: a linear FcRn independent pathway representing typical proteolysis common to all immunoglobulins, and a nonlinear elimination pathway driven by binding to the FcRn target. The model was described by the set of equations ([Equation 1](#)):

Equation 1. Structural Population Pharmacokinetics Model, Rozanolixizumab

$$\begin{aligned}
 K_a &= \frac{1}{MAT} \\
 K_e &= \frac{CL/F}{V/F} \\
 \text{Complex} &= \frac{(K_d \cdot V/F + TA + FcRn_{tot}) - \sqrt{(K_d \cdot V/F + TA + FcRn_{tot})^2 - (4 \cdot TA \cdot FcRn_{tot})}}{2} \\
 \frac{dA_1}{dt} &= -K_a \cdot A_1 \\
 \frac{dA_2}{dt} &= K_a \cdot A_1 - K_e \cdot A_{2,free} - K_{deg} \cdot \text{Complex}
 \end{aligned}$$

Source: FDA Reviewer.

where A1 is the total amount of rozanolixizumab in the depot compartment, K_a is the absorption rate constant following the SC administration of rozanolixizumab, MAT is the mean absorption time, A2 is the total amount of rozanolixizumab in the central compartment, FcRn independent CL/F is the FcRn independent apparent clearance, V/F is the apparent volume of distribution, K_e describes the elimination rate constant of the free drug in the central compartment A2,free which is FcRn independent, K_{deg} is the receptor degradation rate constant, assumed complex is degraded with the same rate based on this approximation, K_d is the dissociation constant, FcRn_{tot} is the estimated total FcRn, TA is total rozanolixizumab with consideration of surface bound FcRn. Interindividual variability (IIV) was evaluated on all parameters and was generally added in an exponential form. The starting residual unexplained variability (RUV) model was a combined error model.

An indirect-response model, where target binding increased the elimination rate of total IgG, was used to describe the turnover of IgG. Rozanolixizumab plasma concentrations and IgG serum concentrations were modelled simultaneously. The effect on IgG elimination was assumed to be related to the degree of target occupancy ([Equation 2](#)).

Equation 2. Indirect Response Model, Rozanolixizumab

$$\begin{aligned}\frac{dIgG}{dt} &= K_{in} - IgG \cdot K_{out} \cdot (1 + ER_{ij}) \\ K_{in} &= K_{out} \cdot \text{Baseline IgG} \\ FcRn_{bound} &= \frac{\text{Complex}}{FcRn_{tot} \cdot V/F} \\ ER_{ij} &= E_{max} \cdot FcRn_{bound}\end{aligned}$$

Source: FDA Reviewer.

where K_{in} is the zero-order rate input, K_{out} is the first-order elimination rate constant, ER_{ij} is the rozanolixizumab effect as fractional increase in K_{out} , for subject i , at time point j , E_{max} is the maximum effect (i.e., maximum fractional increase in K_{out}), FcRn_{tot} is the estimated total FcRn, FcRn_{bound} is the estimated bound FcRn as a fraction from 0 to 1. All model parameters were estimated. IIV was evaluated on all parameters and was generally added in an exponential form. The starting RUVmodel was a proportional error model.

The starting point for the covariate model building was the base PK-IgG model. The covariate (study population, age, body weight, sex, race, baseline steroid usage, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, antidrug antibodies, neutralizing antibodies (NAb)-parameter (FcRn independent CL/F, V/F, MAT, baseline IgG, K_{out} , and E_{max}) relationships were evaluated for inclusion in the model. Structural covariates were tested by full fixed effects model (FFEM) where all the prespecified covariate-parameter relationships were included in the model in one step, followed by a backward elimination step of parameters with high relative standard error (relative standard error >70%). Exploratory covariates were tested by the stepwise covariate model building procedure with adaptive scope reduction.

PK/ PD MG-ADL Modeling

The modeling approach was guided by the graphical analysis and consisted of a placebo effect model and a drug effect model. The rozanolixizumab effect on MG-ADL score was linked to IgG inhibition.

The covariate modeling for the PK/PD model for MG-ADL score followed the same principles as for the PK-IgG model. Exploratory covariates (baseline IgG concentration, age, sex, region, stratification factor (MuSK+ or AChR+), baseline steroid usage, duration of disease at baseline, thymectomy at baseline, and Myasthenia Gravis Foundation of America disease class at baseline) were evaluated for inclusion in the model. Exploratory covariates were only considered for parameters associated with IIV terms. The discrimination between models was mainly based on the inspection of graphical diagnostics and changes in the objective function value.

Covariates that had a statistically significant impact on the PK-IgG model parameters were body weight on FcRn independent CL/F, V/F, and baseline IgG, presence of antidrug antibodies /NAb on FcRn independent CL/F, formulation on MAT, ITP patient on V/F, and baseline steroid use on baseline IgG and E_{max} . The final parameter estimates are shown in [Table 87](#).

Table 87. Parameter Estimates of the Applicant's Final and Base PopPK-IgG Model

		Base PK-IgG model			Final PK-IgG model		
Run		4			14		
OFV		12087.39			11731.70		
Condition number		75.73			93.18		
		Base PK-IgG model			Final PK-IgG model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
FcRn independent CL/F	L/day	0.878	13.4		0.888	12.5	
V/F	L	7.17	5.74		6.64	4.90	
MAT	day	1.53	7.62		1.84	6.59	
IgG baseline	g/L	10.0	1.37		10.7	1.72	
FcRn _{tot}	nmol/L	161	5.32		163	5.06	
K _d	day ⁻¹	2.03	9.54		2.07	9.12	
K _{deg}	day ⁻¹	0.520	4.91		0.550	4.34	
IgG half-life	day	18.1	3.76		18.8	4.01	
E _{max}		3.67	3.65		3.24	4.49	
PK Prop. RUV	(CV)	0.376	3.27		0.368	3.12	
PK Add. RUV	nmol/L	1.99	3.88		1.91	3.53	
PD Prop. RUV	(CV)	0.112	0.272		0.113	0.283	
Weight on FcRn independent CL/F					1.32	21.8	
Weight on V/F					0.819	8.11	
Weight on IgG baseline					-0.155	31.7	
							(b) (4)
ADA +ve/ NAb -ve on FcRn independent CL/F					-0.322	23.8	
ADA +ve/ NAb +ve on FcRn independent CL/F					1.64	20.8	
Steroids on IgG baseline					-0.165	12.8	
Steroids on E _{max}					0.271	25.4	
							(b) (4)
IIV FcRn independent CL/F	(CV)	1.02	11.0	49.9	0.546	19.3	63.1
IIV V/F	(CV)	0.362	5.88	17.4	0.247	5.79	23.5
IIV MAT	(CV)	0.542	7.02	32.4	0.485	7.37	31.8
IIV IgG baseline	(CV)	0.255	4.07	1.19	0.233	3.96	2.13
IIV IgG half-life	(CV)	0.425	3.50	9.53	0.441	4.03	12.0
IIV E _{max}	(CV)	0.399	5.22	14.8	0.387	5.53	15.5

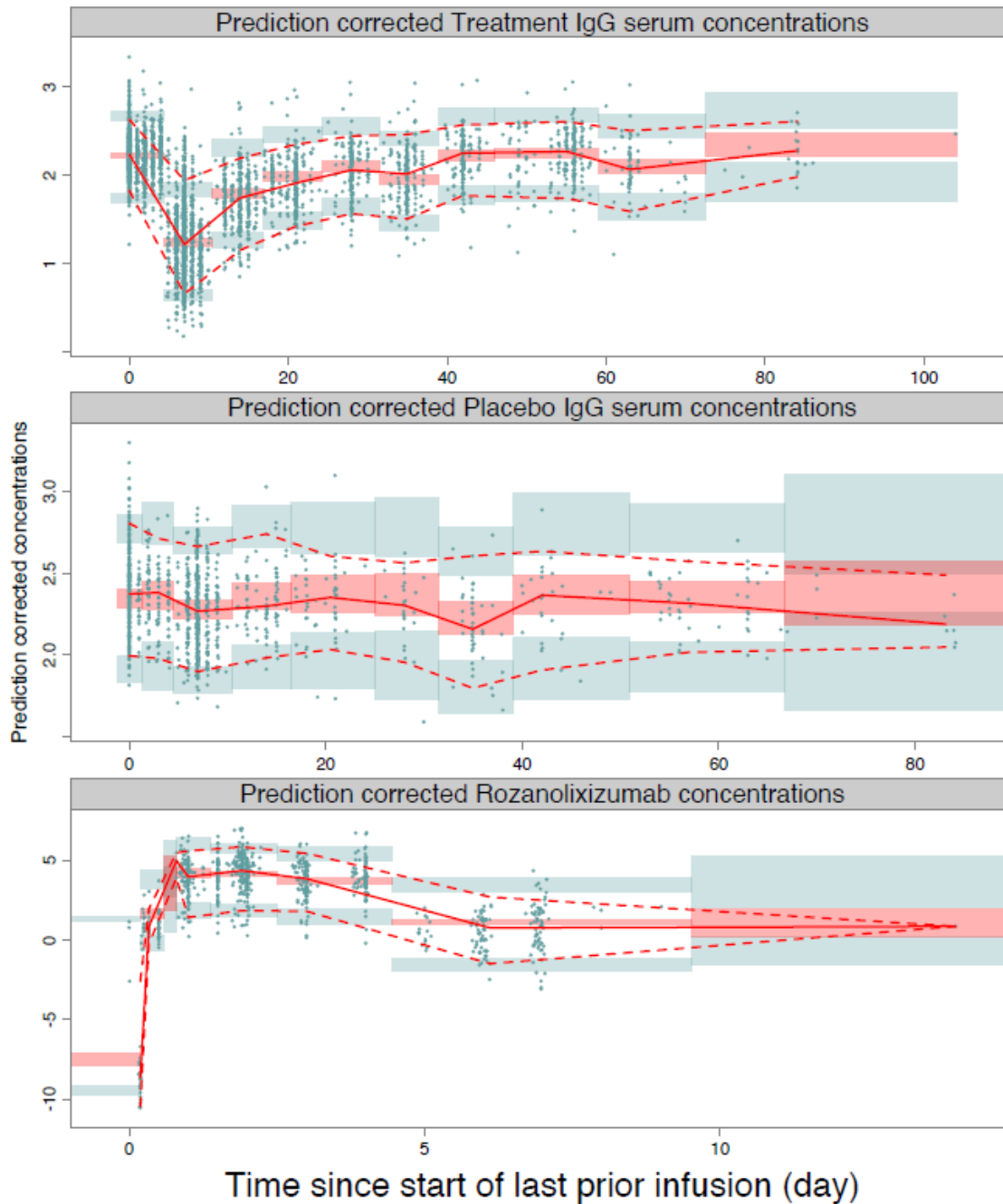
Source: The Applicant's popPK report cl0534 Page 65, Table 14

The RSE for IIV and RUV parameters are reported on the approximate SD scale

Abbreviations: +ve, positive; -ve, negative.; ADA, antidrug ant body; Emax, maximum effect; FcRn, neonatal fragment crystallizable receptor; FcRntot, estimated total neonatal fragment crystallizable receptor; IgG, immunoglobulin G; Kd, dissociation constant; Kdeg, receptor degradation rate constant; MAT, mean absorption time; NAb, neutralizing antibodies; OFV, objective function value; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population pharmacokinetics; RSE relative standard error; RUV, residual unexplained variability

For a typical 76 kg subject (median body weight in the dataset), the estimated linear FcRn independent CL/F and V/F were 0.89L/day and 6.6L, respectively. The popPK/PD model was assessed with diagnostics plots including goodness-of-fit and prediction corrected visual predictive check ([Figure 21](#) and [Figure 22](#)).

Figure 21. Prediction Corrected Visual Predictive Check (pcVPC) of Log-Transformed Rozanolixizumab and IgG Concentrations Versus Time Since Last Dose, Stratified by Groups: Placebo and Treatment, Based on 500 Simulated Data Sets, Using the Final PK-IgG Model

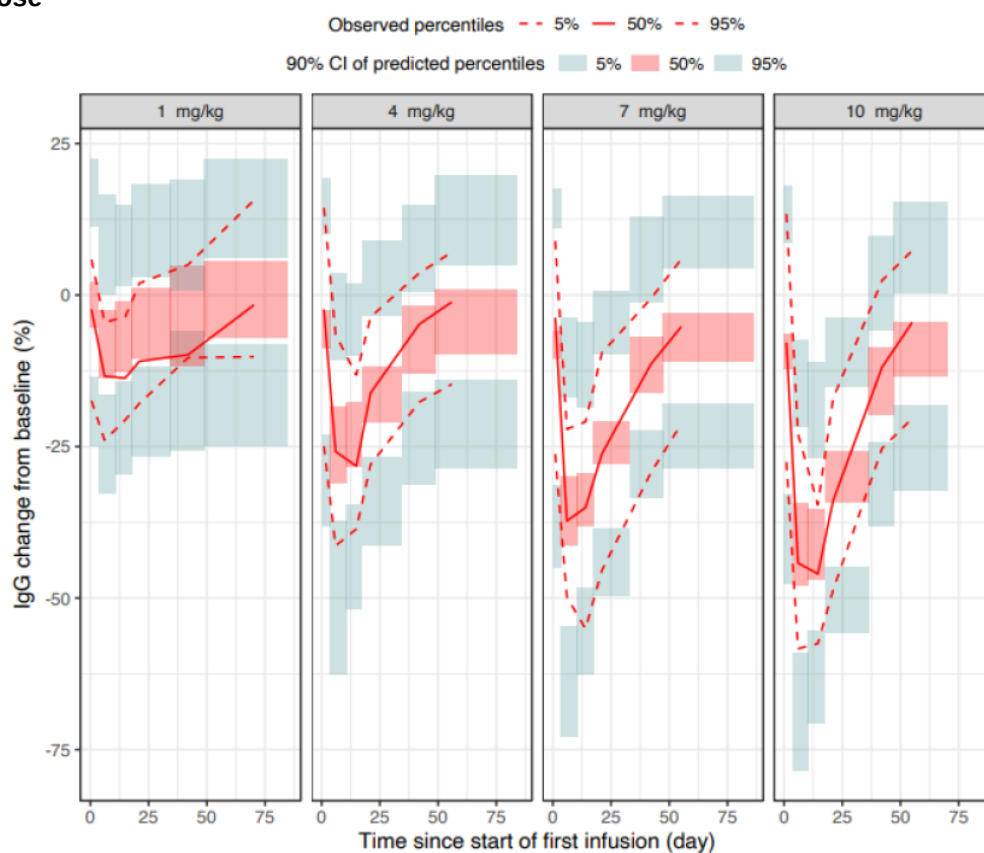


Source: The Applicant's popPK report cl0534 Page 66, Figure 25

Note: Individual prediction corrected observations are indicated by green dots. The solid and dashed red lines represent the median, 5th and 95th percentiles of the prediction corrected observations; the shaded pink and green areas represent the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model.

Abbreviations: IgG, immunoglobulin G; pcVPC, prediction corrected visual predictive check; PK, pharmacokinetic; PopPK, population pharmacokinetics

Figure 22. Visual Predictive Check of Percent Change From Baseline IgG Versus Time, for Studies UP0018 and UP0060 in the PK-IgG Analysis Data Set Using the Final PK-IgG Model, Stratified by Dose



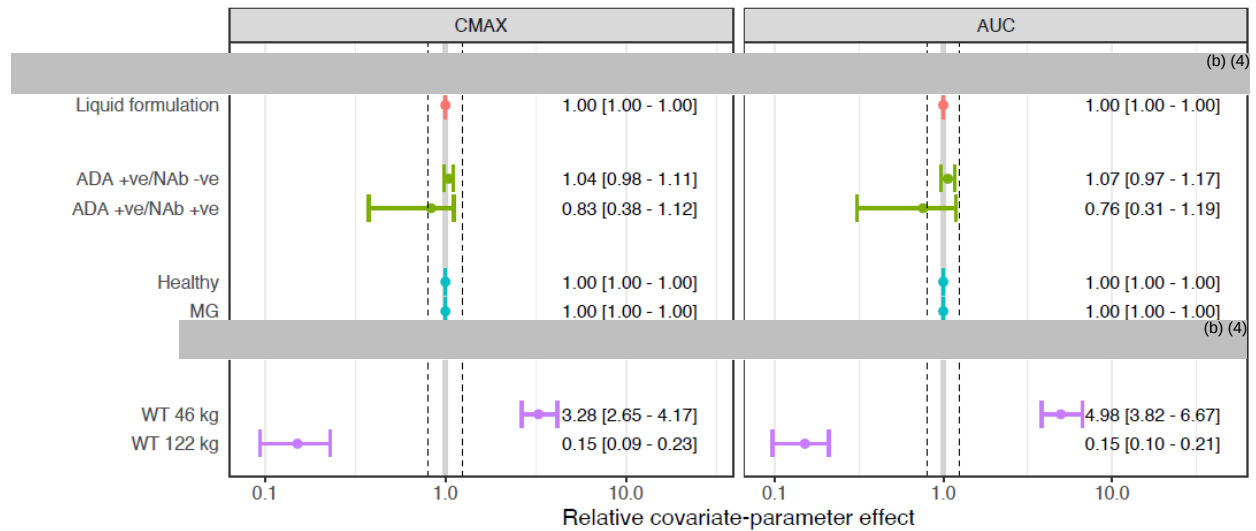
Source: The Applicant's response to Clin Pharm IR dated April 27th, 2023, Figure 1
Abbreviations: IgG, immunoglobulin G; PK, pharmacokinetic

The main findings of the covariate analysis were:

- Body weight (range 37.7 to 156 kg) had a statistically significant impact on the PK-total IgG model parameters of FcRn independent CL/F, V/F, and baseline total IgG. The presence of NAb had a significant impact on FcRn independent CL/F, (b) (4), and baseline steroid use had a significant impact on Baseline total IgG and maximum effect (E_{max}). (b) (4), and baseline steroid use had a significant impact on baseline total IgG and maximum effect (E_{max}).
- The estimated glomerular filtration rate (range 38.2 to 161 mL/min/1.73 m²) and hepatic function tests, including alanine aminotransferase (range 3.00 to 158 U/L), aspartate aminotransferase (range 9.00 to 127 U/L), alkaline phosphatase (range 22.0 to 386 U/L), and bilirubin (range 3.50 to 37.2 U/L), did not exhibit any statistically significant impact on rozanolixizumab CL/F. There are no statistically significant differences in CL/F or V/F between healthy study subjects and gMG patients. Additionally, no statistically significant impact on FcRn independent CL/F, V/F, baseline total IgG, E_{max} , or total IgG half-life was found with sex (57.5% female), race (Asian versus non-Asian), or age (range 18 to 89 years). Additionally, no statistically significant impact on FcRn independent CL/F, V/F, baseline total IgG, E_{max} , or total IgG half-life was found with sex (57.5% female), race (Asian versus non-Asian), or age (range 18 to 89 years).

The effects of the statistically significant covariates on rozanolixizumab exposure at steady state are summarized in the forest plots in [Figure 23](#). The impact of the covariates on the total IgG percentage change from baseline profiles is illustrated in [Figure 24](#) and on the MG-ADL score change from baseline in [Figure 25](#).

Figure 23. Forest Plot Illustrating the Covariate Effects on Rozanolixizumab C_{max} and AUC Ratios as Compared With the Median Reference Patient

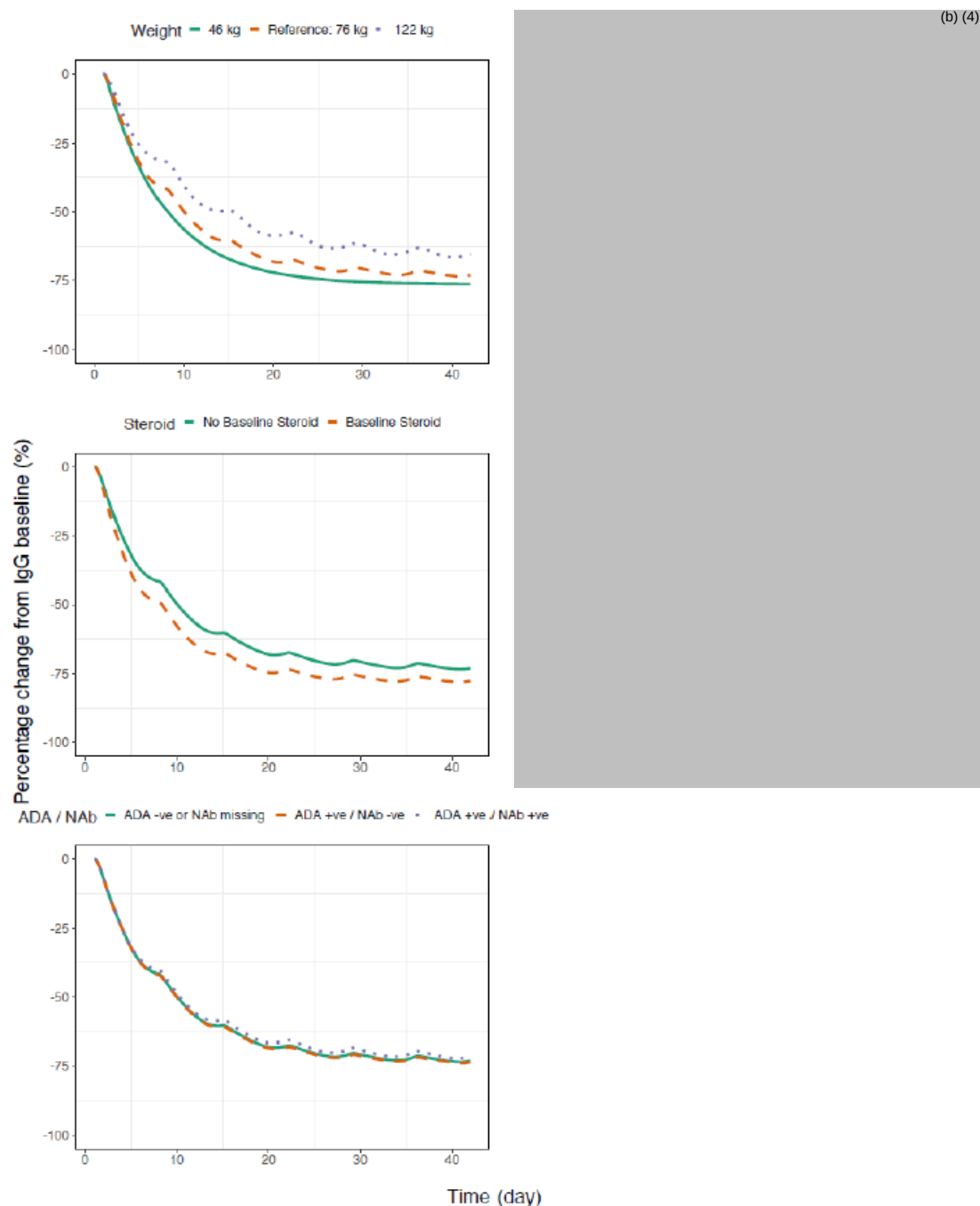


Source: The Applicant's popPK report cl0534 Page 72, Figure 31

Note: The reference patient is a 76 kg patient with MG, -ve ADA and who received the liquid formulation of rozanolixizumab. The closed symbols represent the point estimates and the whiskers represent the 95% CI, based on a nonparametric bootstrap of 500 samples. The vertical gray line is marking no change, and the vertical dashed lines are marking the 0.8 to 1.25 interval. The numbers are point estimate [95% CI] of the change in the parameter compared to the reference patient with the median estimate of each covariate. X-axis is on log scale.

Abbreviations: +ve, positive; -ve, negative; AUC, area under the curve; ADA, antidrug antibody; C_{max}, maximum plasma concentration; ITP, immune thrombocytopenia; MG, myasthenia gravis; NAb, neutralizing antibodies; WT, weight

Figure 24. Impact of Covariates on the Predicted Percentage Change From Total IgG Baseline



Source: The Applicant's popPK report cl0534 Page 77, Figure 36

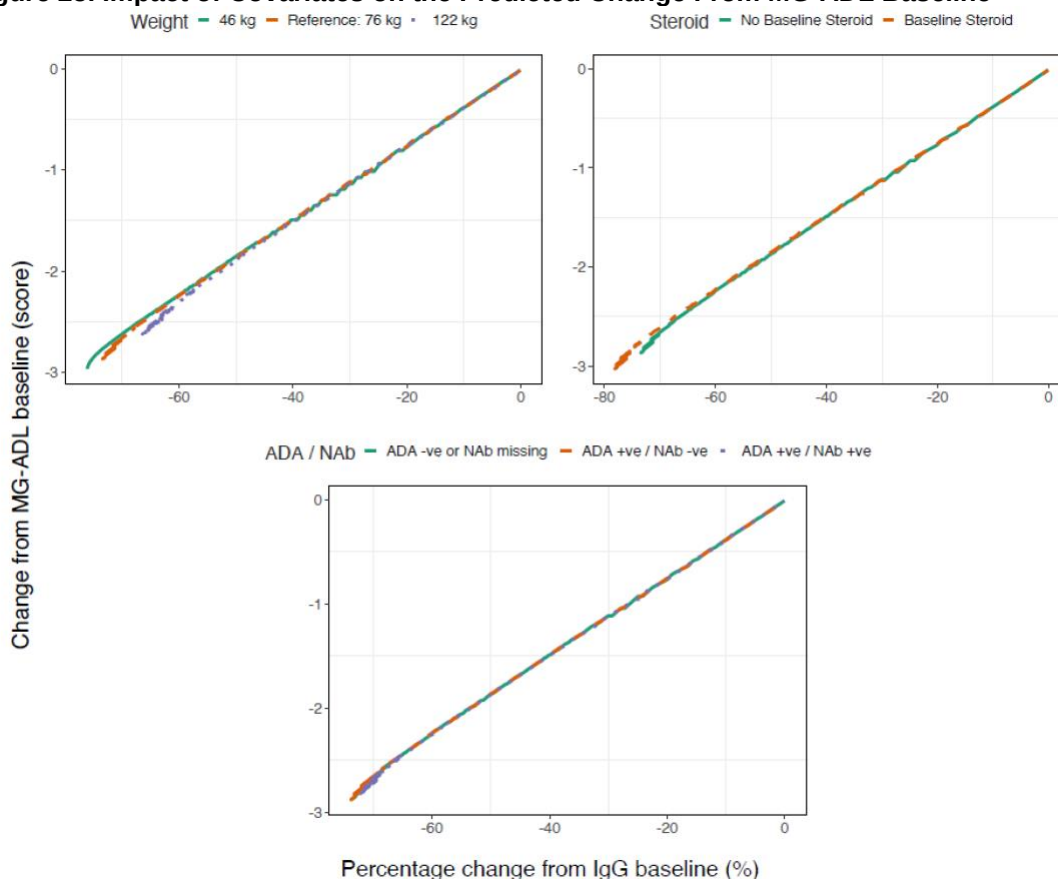
Note: The impact of patient-specific covariates on the predicted percentage change from total IgG baseline is based on the final PK-total IgG model, following the administration of 6 doses of rozanolixizumab 560 mg.

Note: The reference patient is a 76 kg patient with MG, -ve ADA, and who received the liquid formulation of rozanolixizumab.

Note: For body weight-parameter relation in the final PK-total IgG model, the impact has been shown for the 2.5th and 97.5th percentile of the covariate (across the patients in the analysis data set), and in relation to the median covariate value in the analysis data set.

Abbreviations: +ve, positive; -ve, negative.; ADA, antidrug ant body; IgG, immunoglobulin G; ITP, immune thrombocytopenia; MG, myasthenia gravis; NAb, neutralizing antibodies

Figure 25. Impact of Covariates on the Predicted Change From MG-ADL Baseline



Source: The Applicant's popPK report cl0534 Page 78, Figure 37

Note: Impact of covariate-related predicted change from total IgG baseline on the predicted percentage change from MG-ADL score baseline, following the administration of 6 doses of 560 mg of rozanolixizumab, once a week.

Note: The reference patient is a 76 kg patient with MG, -ve ADA or missing NAb, and who received the liquid formulation of rozanolixizumab.

Note: For body weight-parameter relation in the final PK-IgG model, the impact has been shown for the 2.5th and 97.5th percentile of the covariate (across the patients in the analysis data set), and in relation to the median covariate value in the analysis data set.

Abbreviations: ADA, antidrug antibody; IgG, immunoglobulin G; MG-ADL, myasthenia gravis activities of daily living; NAb, neutralizing antibodies; +ve, positive; -ve, negative.

The final PK/PD model for MG-ADL score parameter estimates are presented in [Table 88](#) and pcVPC is shown in [Figure 26](#).

Table 88. Parameter Estimates of the Applicant's Final PK/PD Model for MG-ADL Score

Final PKPD model for MG-ADL				
Run		9		
OFV		5414.75		
Condition number		5.76		

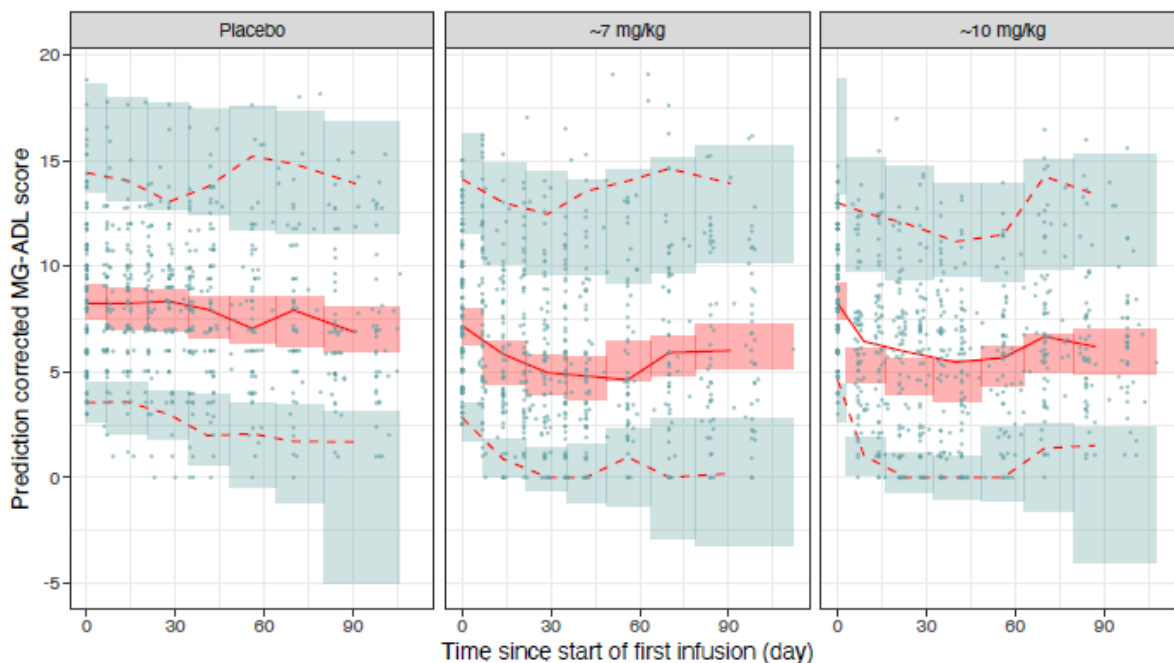
Final PKPD model for MG-ADL				
	Unit	Value	RSE (%)	SHR (%)
MG-ADL score baseline	score	8.26	3.83	
$E_{\max, \text{MG}}$		0.436	19.8	
Placebo	/day	0.000976	14.9	
γ		0.180	30.2	
IIV MG-ADL score baseline	(CV)	0.380	6.13	7.93
IIV $E_{\max, \text{MG}}$	(CV)	3.23	10.4	33.9
IIV Placebo	(CV)	1.30	11.6	27.1
RUV		1.65	0.844	8.18

Source: The Applicant's popPK report cl0534 Page 84, Table 20

The RSE for IIV and RUV parameters are reported on the approximate SD scale $E_{\max, \text{MG}}$ is the maximum effect at an IgG change from baseline of -100%, constrained between 0 and 1, and γ is the effect of Myasthenia Gravis Foundation of America disease class at baseline on baseline MG-ADL.

Abbreviations: CV, coefficient of variation; IIV, interindividual variability; MG-ADL, myasthenia gravis activities of daily living; OFV, objective function value; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error; RUV, residual unexplained variability; SHR, shrinkage

Figure 26. Prediction Corrected Visual Predictive Check (pcVPC) of MG-ADL Scores Versus Time Since the Start of First Dose, Stratified by Dose Group, Based on 200 Simulated Data Sets, Using the Final MG-ADL PK/PD Model



Source: The Applicant's popPK report cl0534 Page 85, Figure 41

Note: Individual prediction corrected observations are indicated by green dots. The solid and dashed red lines represent the median, 5th and 95th percentiles of the prediction corrected observations; the shaded pink and green areas represent the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model.

Abbreviations: MG-ADL, myasthenia gravis activities of daily living; pcVPC, prediction corrected visual predictive check; PD, pharmacodynamic; PK, pharmacokinetic

The Applicant used the final PK/PD model to compare the performance of the phase 3 weight-tiered dosing regimen and a simple 2-fixed dosing regimen in terms of exposure, total IgG reduction, disease-specific autoantibody reduction, and MG-ADL response. Additionally, simulations were conducted to assess the treatment strategy in case of a missed or delayed dose by analyzing the PK and total IgG profiles.

Simulations were performed using PK-total IgG and AChR mg-ADL models to predict outcomes of 2-fixed dosing and compare them with the phase 3 weight-tiered dosing regimen. These simulations were carried out for an MG population by sampling subject characteristics from MG0003 or for specific body weight groups. Two dosing regimens were compared after a 6-week cycle: a 2-fixed dose regimen and the weight-tiered regimen studied in the phase 3 gMG program. Six weekly doses were simulated for each regimen ([Table 36](#) in Section [II.6.3.3](#)).

The 2-fixed dose regimen resulted in predicted rozanolixizumab $C_{max,ss}$ almost equivalent to the weight-tiered dose regimen of ≈ 7 mg/kg or ≈ 10 mg/kg for the overall MG population. However, for subjects with a body weight of 100 kg or more, the simulated exposure with the 2-fixed dose was significantly lower compared to the lowest studied dose of 7 mg/kg.

The distribution of $C_{max,ss}$ with the ≈ 7 mg/kg, ≈ 10 mg/kg and 2-fixed dose regimens was compared by weight tier to investigate the influence of extreme body weights on exposure ([Figure 27A](#) and [Figure 28A](#)).

According to the Applicant, the simulation results suggested that the weekly doses of rozanolixizumab approximating 7 mg/kg, 10 mg/kg and 2-fixed dose regimens for 6 consecutive weeks were indicative of potentially achieving mean maximum total IgG reductions of $\geq 70\%$ ([Figure 27B](#) and [Figure 28B](#)).

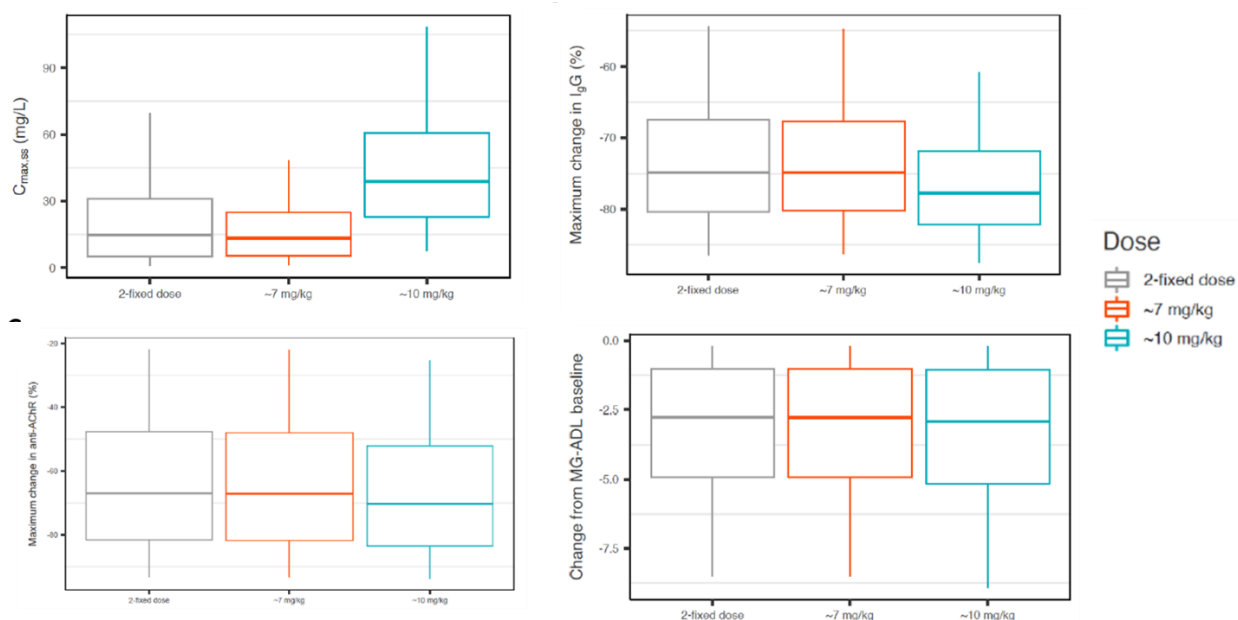
To compare the simulated PD between the 2-fixed dosing and weight-tiered dosing, minimum anti-AChR concentration (nadir), maximum percentage change from baseline anti-AChR, and AUEC (area under the curve) for percentage change from baseline anti-AChR were assessed for the overall MG population and stratified by weight tier.

According to the Applicant, the simulations demonstrated that in the overall MG population ([Figure 27C](#), [Figure 28C](#), and [Table 89](#)), the 2-fixed dose regimen achieved a median maximum anti-AChR reduction from baseline of 67.0%. This reduction was comparable to that achieved with the ≈ 7 mg/kg weight-tiered dosing (67.2%) and slightly lower than the ≈ 10 mg/kg weight-tiered dose (70.3%). The maximum percentage change from baseline anti-AChR remained consistent across all regimens, as confirmed by simulations based on anti-AChR nadir and AUEC. Among patients weighing ≥ 100 kg, the 2-fixed dose regimen achieved the smallest median maximum percentage anti-AChR reduction of 62.8%.

To compare the efficacy between 2-fixed dosing and weight-tiered dosing, the changes from baseline in MG-ADL score on day 43 were simulated for both regimens using the total IgG-MG-ADL and AChR-MG-ADL models. Both models yielded similar predictions for MG-ADL response.

Based on the Applicant's simulation, in the overall MG population, the 2-fixed dose regimen achieved a mean predicted MG-ADL score change from baseline of -3.31 , which was the same as that achieved with the ≈ 7 mg/kg weight-tiered dosing (-3.31) and slightly lower than that for the ≈ 10 mg/kg weight-tiered dose (-3.47) ([Figure 27D](#), [Figure 28D](#) and [Table 89](#)). Across all weight tiers, all dose regimens were predicted to achieve a mean change from baseline MG-ADL score of at least -3.08 , and distribution of the MG-ADL change from baseline values largely overlapped in all regimens ([Table 89](#)).

Figure 27. Box Plots of Predicted $C_{max,ss}$ (A), Maximum Percent Change in Baseline Total IgG (B), Maximum Percent Change In Baseline Anti-AChR (C), and Change from Baseline MG-ADL Score at Day 43 in the MG Population Following SC Administration of the 2-Fixed Dose and Weight-Tiered ≈ 7 mg/Kg and ≈ 10 mg/Kg Doses



Source: The Applicant's popPK report cl0535 Figure 3 (Page 18), Figure 16 (Page 25), Figure 22 (Page 28) and popPK report cl0563 Figure 7 (Page 20)

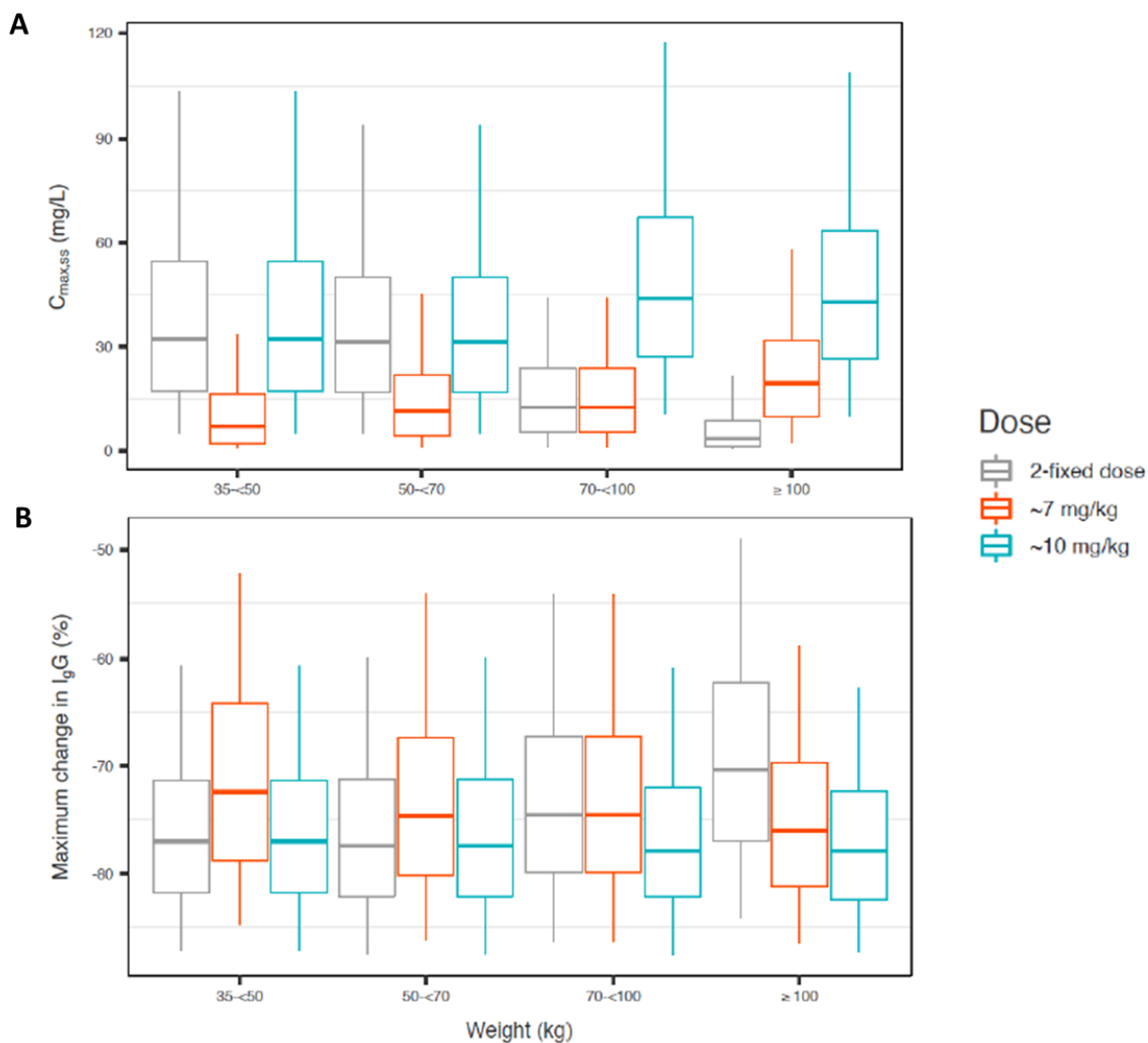
Note: Doses for the 2-fixed dose regimen are 420 mg in patients weighing <50 kg and (b) (4) Q1W). For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈ 7 mg/kg: 35 to <50 kg: 280 mg, 50 to <70 kg: 420 mg, 70 to <100 kg: 560 mg, ≥ 100 kg: 840 mg; for ≈ 10 mg/kg: 35 to <50 kg: 420 mg, 50 to <70 kg: 560 mg, 70 to <100 kg: 840 mg, ≥ 100 kg: 1120 mg).

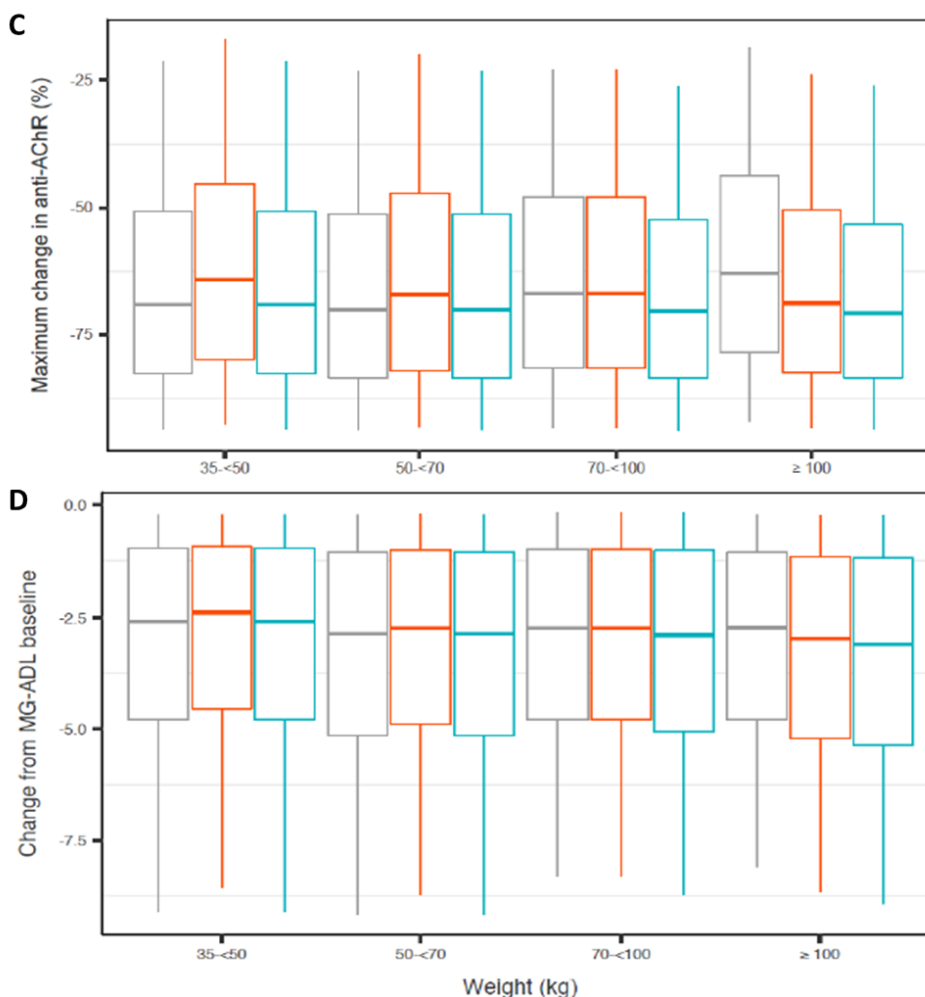
Note: Six weekly doses were simulated for each dosing regimen.

Note: The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and the 75th percentiles, and whiskers extend between the 5th and the 95th percentiles.

Abbreviations: AChR, acetylcholine receptor; $C_{max,ss}$, maximum plasma concentration at steady-state; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; SC, subcutaneous; $\approx/\approx$ =approximate dose

Figure 28. Box Plots of Predicted $C_{max,ss}$ (A), Maximum Percent Change in Baseline Total IgG (B), Maximum Percent Change In Baseline Anti-AChR (C), and Change from Baseline MG-ADL Score at Day 43 Following SC Administration of the 2-fixed Dose and Weight-Tiered ≈ 7 mg/kg and ≈ 10 mg/kg Doses, Stratified by Weight Tier





Source: The Applicant's popPK report cI0535 Figure 4 (Page 18), Figure 17 (Page 26), Figure 23 (Page 29) and popPK report cI0563 Figure 8 (Page 25)

Note: Doses for the 2-fixed dose regimen are 420 mg in patients weighing <50 kg and (b) (4) Q1W). For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈7 mg/kg: 35 to <50 kg: 280 mg, 50 to <70 kg: 420 mg, 70 to <100 kg: 560 mg, ≥100 kg: 840 mg; for ≈10 mg/kg: 35 to <50 kg: 420 mg, 50 to <70 kg: 560 mg, 70 to <100 kg: 840 mg, ≥100 kg: 1120 mg).

Note: Six weekly doses were simulated for each dosing regimen.

Note: The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and the 75th percentiles, and whiskers extend between the 5th and the 95th percentiles.

Abbreviations: ≈/=approximate dose; AChR, acetylcholine receptor; $C_{max,ss}$, maximum plasma concentration at steady-state; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; SC, subcutaneous

Table 89. Predicted PK, Total IgG, Anti-AChR, and MG-ADL Parameters in the gMG Population for 2-Fixed and Weight-Tiered Dose Regimens

Variable Regimen	Mean	Median	5th percentile	95th percentile
C_{max,ss} (mg/L)				
2-fixed dose	22.17	14.69	0.87	69.45
≈7mg/kg	17.45	13.27	1.16	48.38
≈10mg/kg	45.90	38.81	7.54	108.47
AUC_{ss} (mg·day/L)				
2-fixed dose	88.68	42.49	2.96	337.12
≈7mg/kg	60.90	37.93	3.84	196.02
≈10mg/kg	207.50	153.51	20.82	586.68
Maximum percent change from Baseline total IgG				
2-fixed dose	-73.15	-74.88	-86.42	-54.39
≈7mg/kg	-73.21	-74.82	-86.29	-54.74
≈10mg/kg	-76.39	-77.70	-87.48	-60.84
Maximum percent change from Baseline for anti-AChR autoantibodies				
2-fixed dose	-63.36	-66.95	-93.36	-21.81
≈7mg/kg	-63.57	-67.23	-93.34	-22.02
≈10mg/kg	-66.16	-70.32	-93.79	-25.39
Change from Baseline MG-ADL score on Day 43				
2-fixed dose	-3.31	-2.75	-8.51	-0.20
≈7mg/kg	-3.31	-2.76	-8.51	-0.20
≈10mg/kg	-3.47	-2.90	-8.91	-0.21

Source: The Applicant's popPK report cl0535 Page 30, Table 4 and c 0563 report Page 30, Table 4

Note: Doses for the 2-fixed dose regimen are 420 mg in patients weighing <50 kg and (b) (4) Q1W).

For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈7 mg/kg: 35 to <50 kg: 280 mg, 50 to <70 kg: 420 mg, 70 to <100 kg: 560 mg, ≥100 kg: 840 mg; for ≈10 mg/kg: 35 to <50 kg: 420 mg, 50 to <70 kg: 560 mg, 70 to <100 kg: 840 mg, ≥100 kg: 1120 mg).

Note: Six weekly doses were simulated for each dosing regimen.

Note: MG-ADL score predictions presented are based on total IgG mg-DL model. Predictions based on AChR mg-ADL were similar. Abbreviations: AChR, acetylcholine receptor; AUC_{ss} area under the curve at steady state; C_{max,ss}, maximum plasma concentration at steady-state; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; PK, pharmacokinetic; SC, subcutaneous; ≈, approximate dose

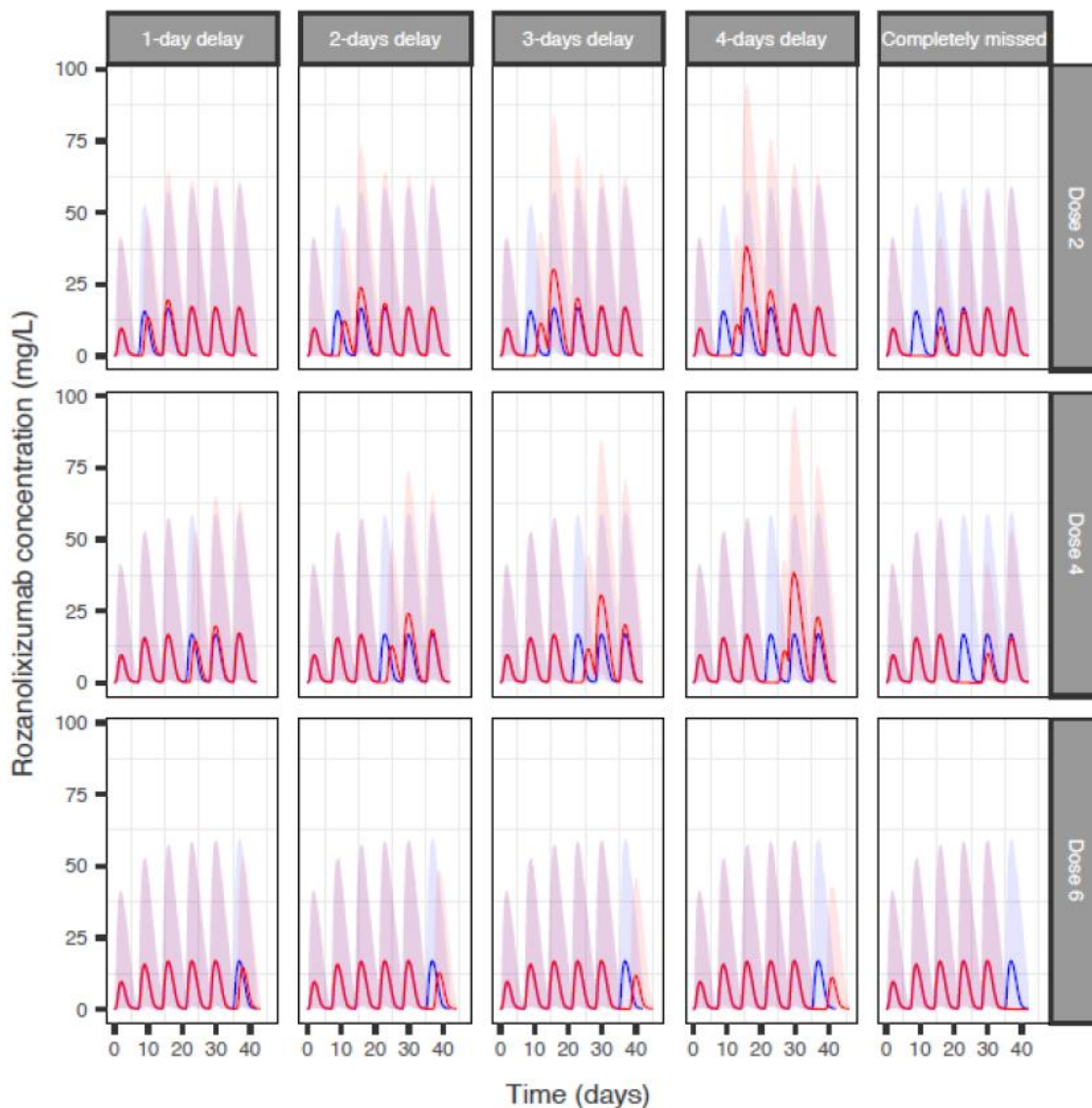
Simulations for Missed or Delayed Dose

The Applicant conducted simulations using the PK-total IgG model to predict the effect of delayed or missed doses on rozanolixizumab plasma concentration profile and total IgG response. The reference dosing regimen was weekly dosing of 560 mg rozanolixizumab for 6 weeks. Scenarios where 1 dose was delayed by 1 to 4 days or skipped were included in the

simulations, with all other doses administered on the planned days, resulting in a shorter interval between consecutive doses the longer the delay.

[Figure 29](#) and [Figure 30](#) illustrate the effect of a missed dose, or a delay of 1 to 4 days for the second, fourth, and sixth dose on rozanolixizumab concentrations and total IgG levels.

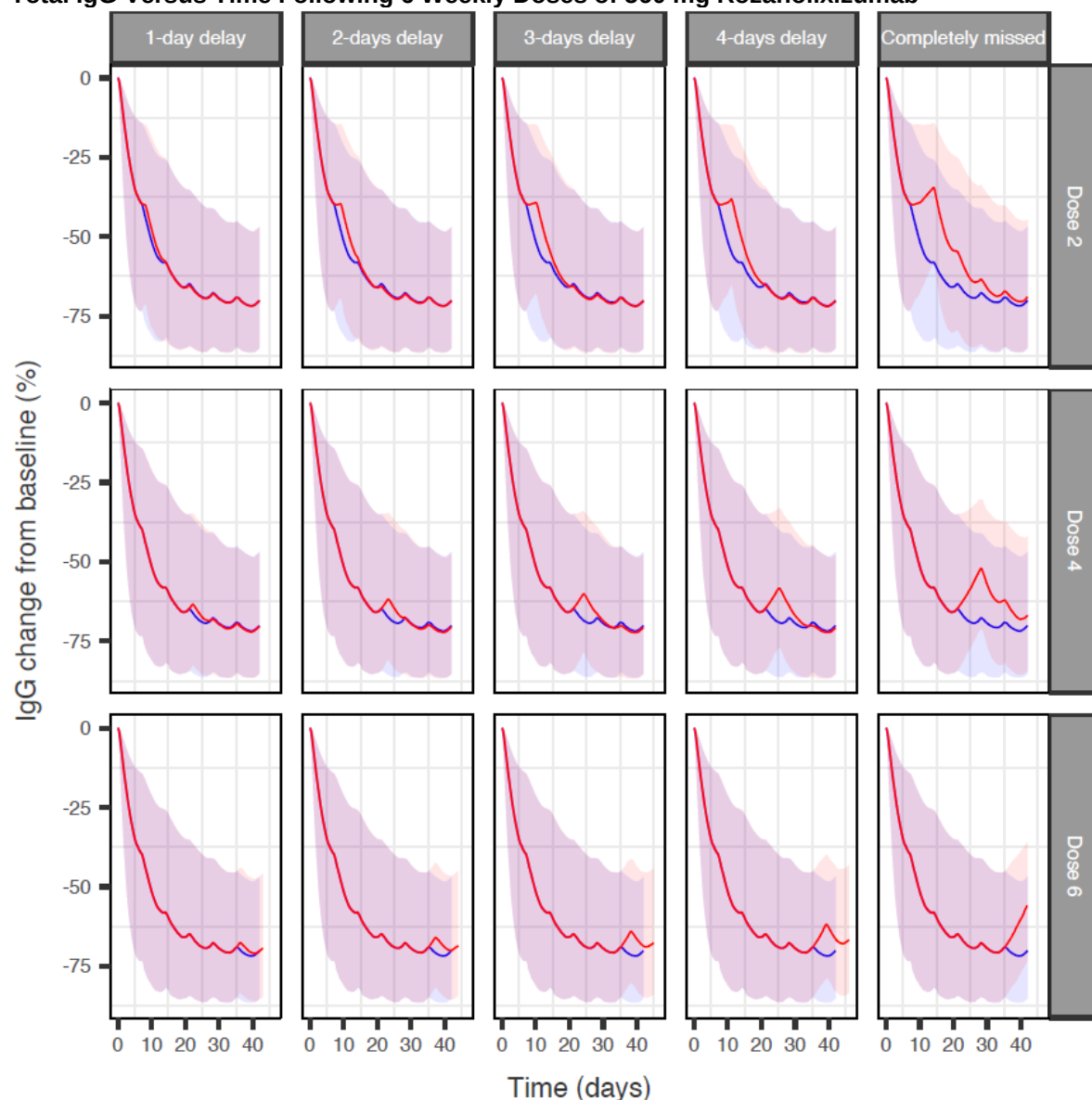
Figure 29. Simulations of Missed or Delayed Dose Scenarios for Rozanolixizumab Plasma Concentration Versus Time Following 6 Weekly Doses of 560 mg Rozanolixizumab



Source: The Applicant's popPK report CL0534 report addendum, Page 22, Figure 10

Note: Stratification by the number of delayed days is done on the X-axis and by the dose number affected by the delay on the Y-axis. The reference scenario (administering all doses as scheduled) is colored in blue and scenarios exploring missed or delayed doses are in red in each stratification. The dose following a delayed dose is taken as originally planned, making the time shorter between the delayed dose and the next. Solid lines represent medians and shaded areas represent the 95th prediction intervals.

Figure 30. Simulations of Missed or Delayed Dose Scenarios for Percent Change from Baseline In Total IgG Versus Time Following 6 Weekly Doses of 560 mg Rozanolixizumab



Source: The Applicant's popPK report CL0534 report addendum, Page 23, Figure 11

Note: Stratification by the number of delayed days is done on the X-axis and by the dose number affected by the delay on the Y-axis. The reference scenario (administering all doses as scheduled) is colored in blue and scenarios exploring missed or delayed doses are in red in each stratification. The dose following a delayed dose is taken as originally planned, making the time shorter between the delayed dose and the next. Solid lines represent medians and shaded areas represent the 95th prediction intervals. Abbreviations: IgG, immunoglobulin G

The simulation results indicate that a delay of 1 to 4 days in dosing would lead to an incremental increase in peak plasma concentrations compared to scheduled dosing at week 2 or week 4.

The highest predicted median C_{max} was observed for the 4-day delayed dose at 39 mg/L, while scheduled dosing resulted in a median C_{max} of 17 mg/L. However, in all delayed dose scenarios, the C_{max} values did not surpass the median C_{max} attained with the weight-tiered dosing of ≈ 10 mg/kg (39 mg/L).

Delaying dosing up to 4 days resulted in temporary, smaller reductions in total IgG compared to scheduled dosing, but the reduction recovered after 2 additional scheduled doses. The simulation predicted that skipping a dose would have a greater impact on IgG reduction than the delayed-dose scenarios.

Reviewer's Comments: The reviewer was able to replicate the Applicant's findings by executing their final PK/PD model. However, since a substantial proportion of rozanolixizumab plasma concentrations fall below the LLOQ, the impact of excluding these samples on the performance of the PK/PD model remains uncertain. It was observed that at the doses of ≈ 1 mg/kg, ≈ 4 mg/kg, ≈ 7 mg/kg, and ≈ 10 mg/kg, 100%, 90%, 71%, and 53% of rozanolixizumab plasma concentrations, respectively, fell below the lower limit of quantification (LLOQ) ([Table 84](#)).

The exclusion of these samples may result in a notable degree of shrinkage towards typical model predictions for the predicted rozanolixizumab concentrations used in driving the PK/PD relationship, especially when modeling PK alone. This effect becomes particularly pronounced in studies involving low doses in MG patients. Additionally, the estimation of TMDD-related parameters may also be affected by this nonrandom censoring. As a result, we lack confidence in the model's predictive ability.

According to the Applicant's proposed draft label, subjects weighing ≥ 100 kg would receive a fixed dose of (b) (4) mg, (b) (4) compared to the ≈ 7 mg/kg and ≈ 10 mg/kg doses administered in efficacy studies. Although the Applicant concluded that these dose differences would not translate into clinically relevant differences in total IgG levels and the MG-ADL clinical endpoint, it remains uncertain whether the Applicant's PK/PD model possesses sufficient sensitivity to accurately predict changes in total IgG and MG-ADL at lower exposures. Furthermore, anti-AChR Ab data at ≈ 1 mg/kg is not available, since this dose was administered only in healthy volunteers. For subcutaneous administrations with ≈ 1 mg/kg, all PK samples were below limit of quantification and with ≈ 4 mg/kg, majority of PK samples were below LLOQ. Consequently, considering that subjects weighing over 100 kg comprise 23% of the phase 3 study population, we have concerns regarding the potential issue of underdosing. For subjects weighing over 100 kg, the efficacy of rozanolixizumab at the proposed fixed dose regimen of (b) (4) mg cannot be reliably predicted. Therefore, we recommend a dose of 840 mg for subjects weighing over 100 kg, as assessed in the MG0003 study.

14.5.2. Reviewer's Analysis

14.5.2.1. Objectives

- Assess labeling statements based on popPK/PD analyses
- Evaluate the proposed fixed dose regimen
- Evaluate the dosing regimen for missed/delayed dose scenarios

14.5.2.2. Methods

Datasets

Table 90. Datasets Utilized

Study	Name	Link to EDR
UP0018, UP0060, MG0002,TP00 01, MG0003,MGO 004, UP0106	dat-3-ucb- roz- blinded- pmx-1- csvxpt_igg. xpt	\\CDSESUB1\EVSPROD\bla761286\0001\m5\datasets\cl0534\analysis\legacy\datasets\dat-3-ucb-roz-blinded-pmx-1-csvxpt_igg.xpt
MG0003	dat- 3 mgadl- ucb-roz- blinded- pmx-1-csv- xpt.xpt	\\CDSESUB1\EVSPROD\bla761286\0001\m5\datasets\cl0534\analysis\legacy\datasets\dat-3 mgadl-ucb-roz-blinded-pmx-1-csv-xpt.xpt
MG0003	cl0562-dat- 3 mgadl- ucb-fte1- roz-pmx-5- csv.xpt	\\CDSESUB1\EVSPROD\bla761286\0001\m5\datasets\cl0534\analysis\legacy\datasets\cl0562-dat-3 mgadl-ucb-fte1-roz-pmx-5-csv.xpt

Source: Reviewers' table

Software

PopPK/PD model fitting was performed in NONMEM 7.4 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.1.2.

Models

The reviewer utilized the Applicant's final popPK/PD model, which consisted of a one-compartment model with TMDD following the quasi-equilibrium assumption. The individual predicted PK parameters were used for PD simulation. Additionally, an independent analysis was conducted by the reviewer to assess the adequacy of the proposed dosing recommendations.

14.5.2.3. Results

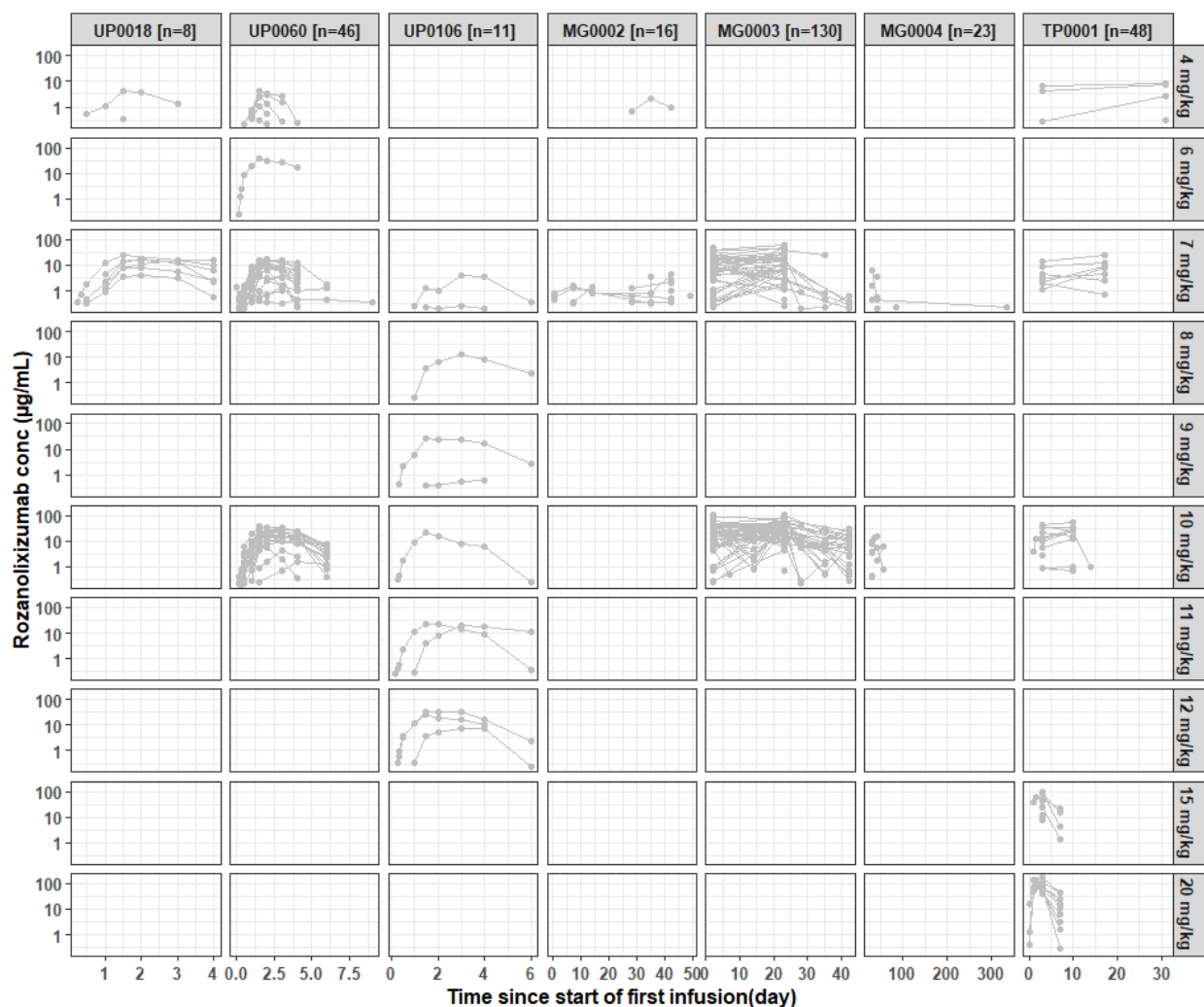
The reviewer achieved comparable results to the Applicant through the execution of the final PK/PD model. In addition to the predictions derived from the popPK/PD model, the reviewer thoroughly examined the observed data and the clinical pharmacology of rozanolixizumab to assess the appropriateness and acceptability of the proposed labeling statements.

Evaluation of PopPK and PopPK/PD Model

Overview of Observed Data

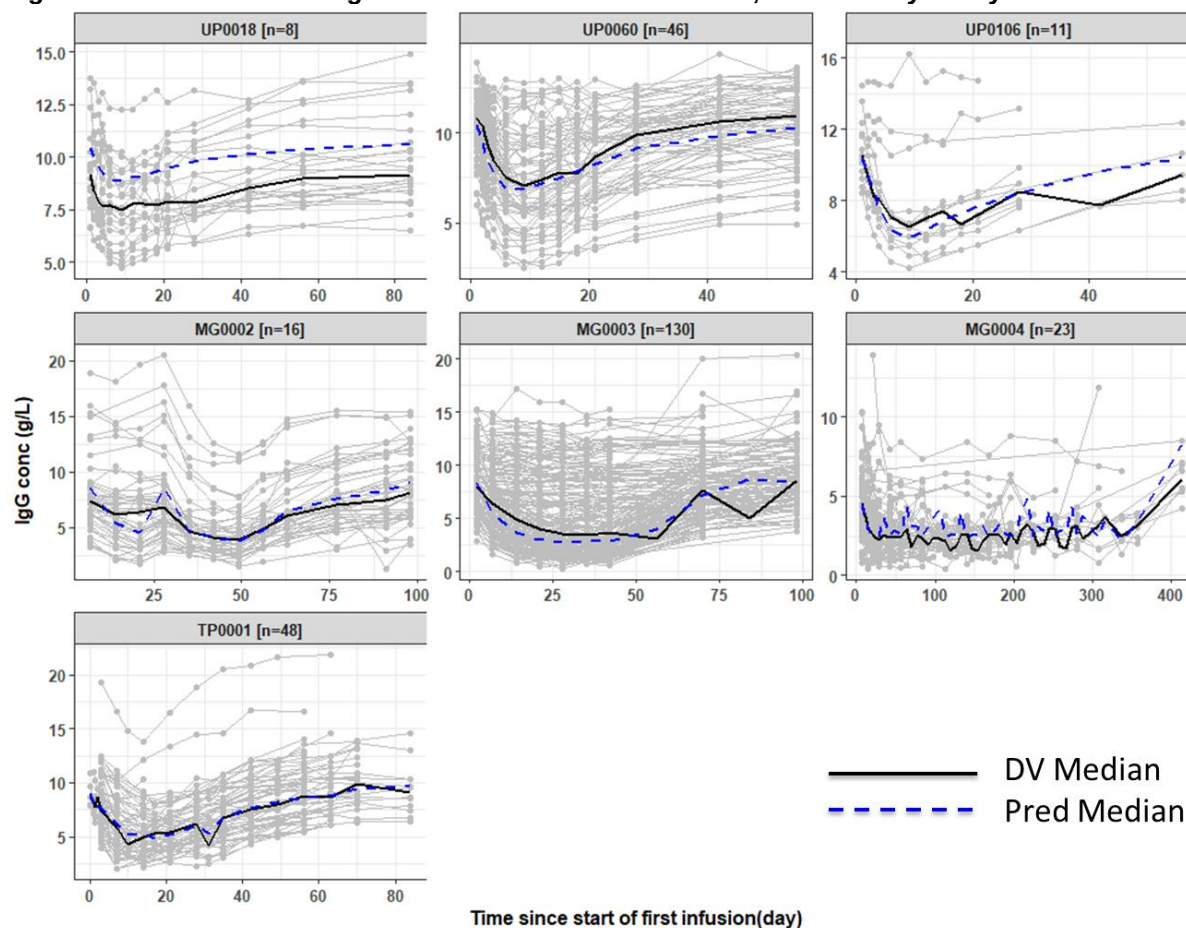
[Figure 31](#) and [Figure 32](#) present PK and IgG profiles of rozanolixizumab across study, respectively.

Figure 31. Observed Plasma Rozanolixizumab Concentrations Versus Time, Stratified by Study and Dose



Source: Reviewer's Analysis.
Abbreviations: conc, concentration

Figure 32. Observed Total IgG Concentrations Versus Time, Stratified by Study

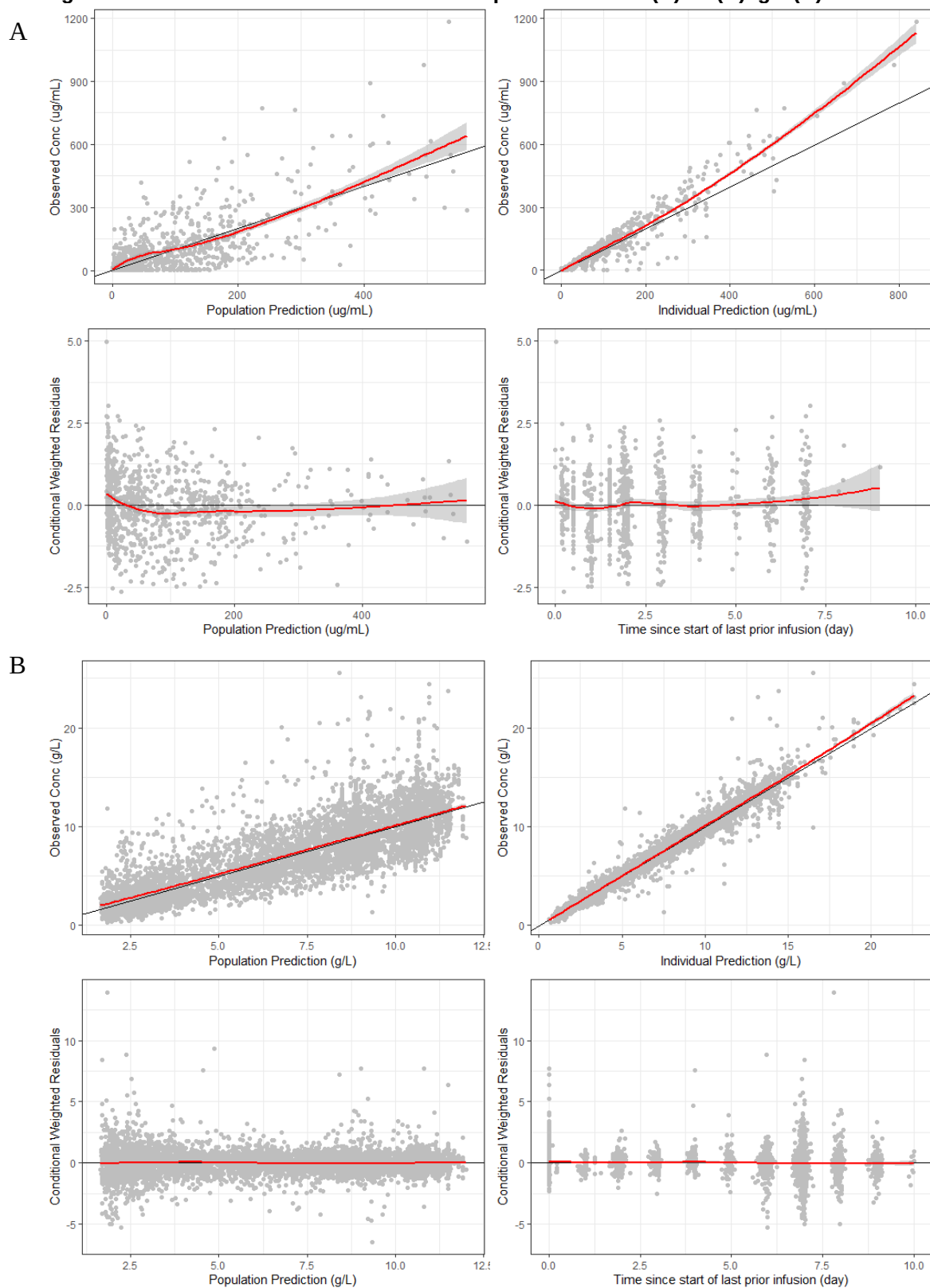


Source: Reviewer's Analysis

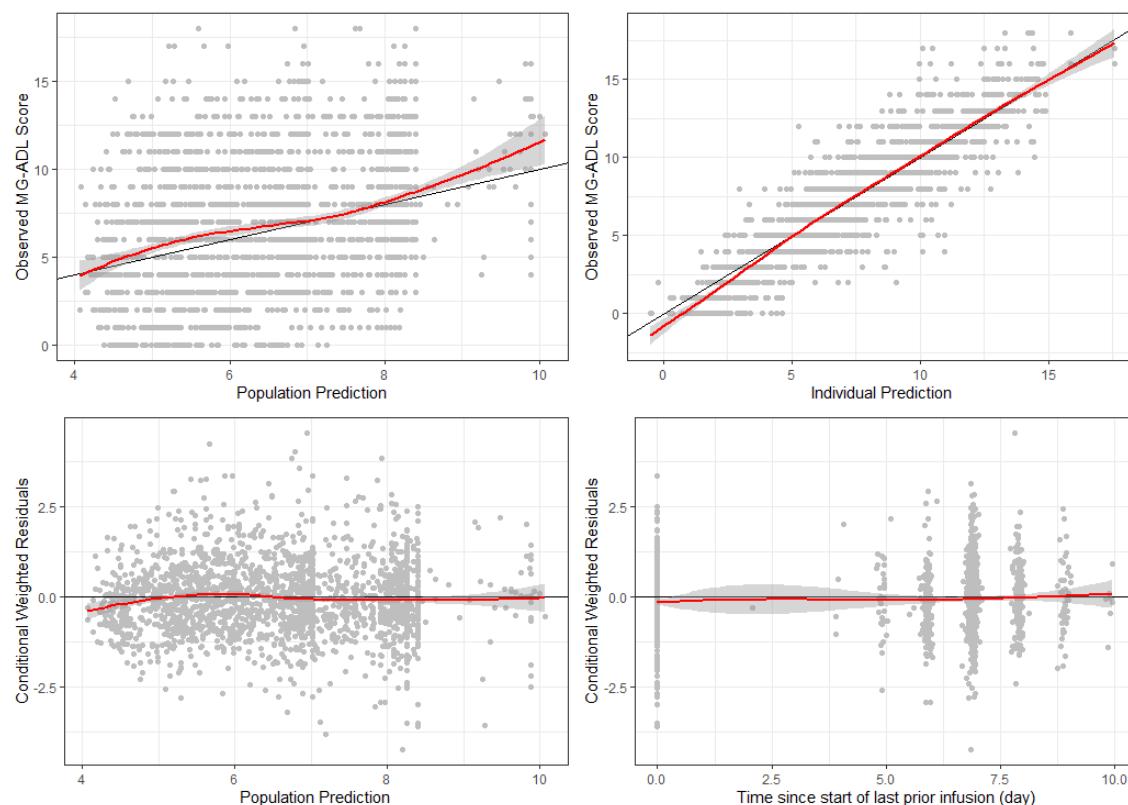
Abbreviations: conc, concentration; DV, dependent variable (observed value); IgG, immunoglobulin G; PRED, population prediction

The reviewer was able to reproduce the model and obtain similar model diagnostics ([Figure 33](#)) for popPK/PD models. PopPK analysis, evaluating the influence of age, sex, race, renal function (estimated glomerular filtration rate [eGFR] 38 to 161 mL/min/1.73 m²), hepatic biochemical and function tests (ALT, AST, alkaline phosphatase and bilirubin) revealed no clinically significant impact of these factors on the pharmacokinetics of rozanolixizumab ([Figure 34](#)).

Figure 33. Goodness-of-Fit Plots for Final PopPK/PD Model: (A)PK (B) IgG (C)MG-ADL Score



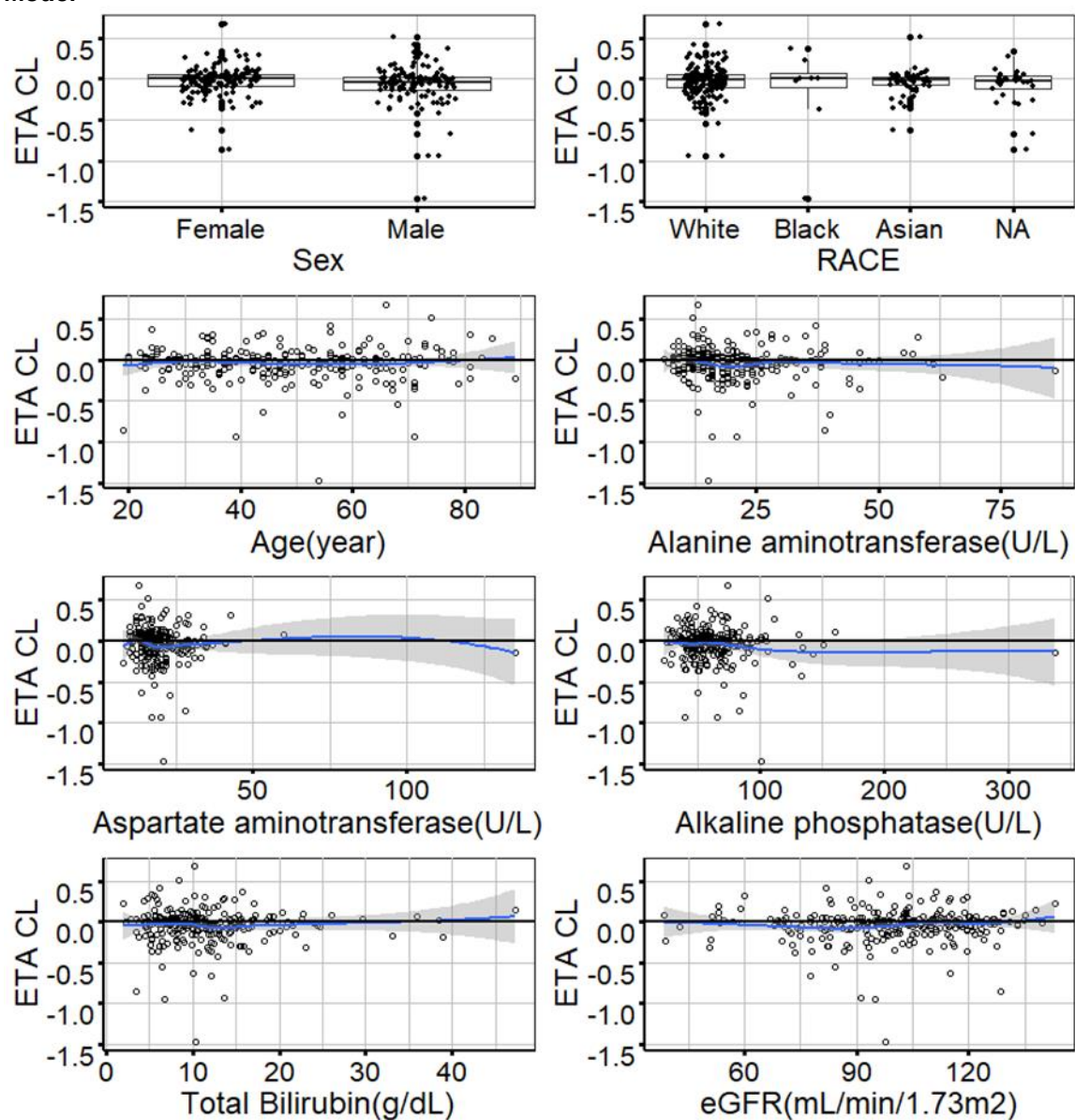
C



Source: Reviewer's Analysis

Note: Values are indicated by points (solid grey) with a loess smooth trend line (solid red) through the data. The line of identity (solid black) is shown as reference.

Abbreviations: conc, concentration; IgG, immunoglobulin G; MG-ADL, myasthenia gravis activities of daily living; PD, pharmacodynamic; PopPK, population pharmacokinetics

Figure 34. ETA Covariate Plots on Clearance Versus Continuous Covariates for Final PopPK/PD Model

Source: Reviewer's Analysis

Abbreviations: CL, clearance; eGFR, estimated glomerular filtration rate; ETA, interindividual variability; PD, pharmacodynamic; PopPK, population pharmacokinetics

Evaluation of Proposed 2-Fixed Dose Regimen

The Applicant's popPK/PD model was used to support fixed dose recommendations for adult patients with generalized myasthenia gravis (gMG). Reviewer conducted PK simulations ([Table 91](#)) using demographic data of subjects with gMG from Study MG0003 (n=163) to generate PK profiles following proposed fixed dose and ≈ 7 mg/kg, ≈ 10 mg/kg dose regimens ([Figure 35](#)).

Table 91. Simulation Scenarios to Compare the Fixed-Dose and Weight-Tiered Dosing Regimens Across Different Bodyweight Group

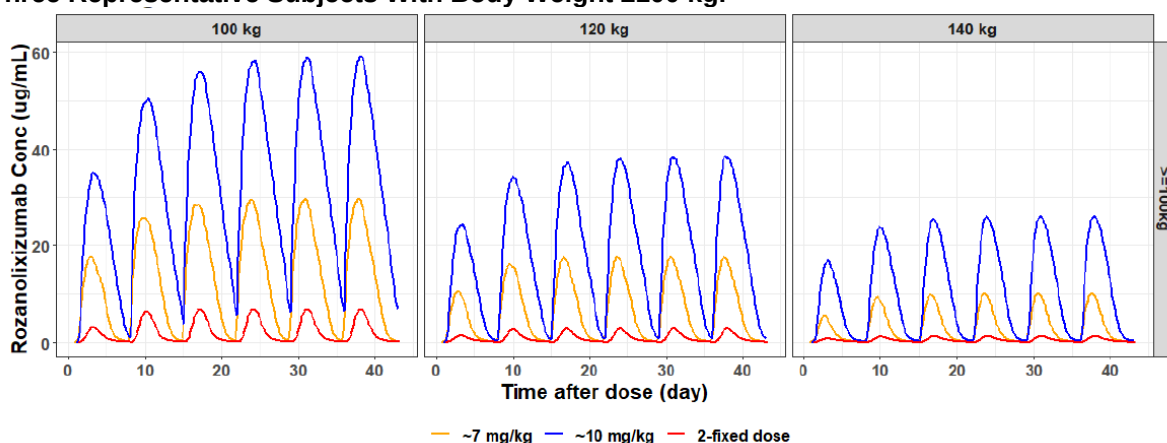
Scenarios	Weight Range (kg)	Dose Regimen	Dose (mg)
1	35 to 50	≈7 mg/kg	280
2	35 to 50	≈10 mg/kg	420
3	35 to 50	2 fixed dose	420
4	50 to 70	≈7 mg/kg	420
5	50 to 70	≈10 mg/kg	560
6	50 to 70	2 fixed dose	(b) (4)
7	70 to 100	≈7 mg/kg	560
8	70 to 100	≈10 mg/kg	840
9	70 to 100	2 fixed dose	(b) (4)
10	≥100	≈7 mg/kg	840
11	≥100	≈10 mg/kg	1120
12	≥100	2 fixed dose	(b) (4)

Source: Reviewer's Analysis

Based on the simulation results, it appears that the simplified two-fixed dosing regimens can yield similar exposure for most body weight groups, except for individuals weighing over 100 kg. For subjects weighing over 100 kg, the median steady-state exposure following the 2-fixed dose regimen ((b) (4) mg) is significantly lower compared to the approximate 7 mg/kg dosing regimen.

In the Applicant's proposed draft label, subjects weighing ≥100 kg would be prescribed a fixed dose of (b) (4) mg, (b) (4) compared to the ≈7 mg/kg and ≈10 mg/kg doses administered in efficacy studies. To further investigate, we simulated the PK profiles for these subjects and observed that the serum concentrations of rozanolixizumab were significantly lower than the lowest studied dose of ≈7 mg/kg (Figure 35).

Figure 35. Simulated Rozanolixizumab Concentrations in Subjects With Body Weight ≥100 kg. Shown Are PK Profiles for Three Dosing Regimens (≈7 mg/kg, ≈10 mg/kg and 2-Fixed Dose) in Three Representative Subjects With Body Weight ≥100 kg.



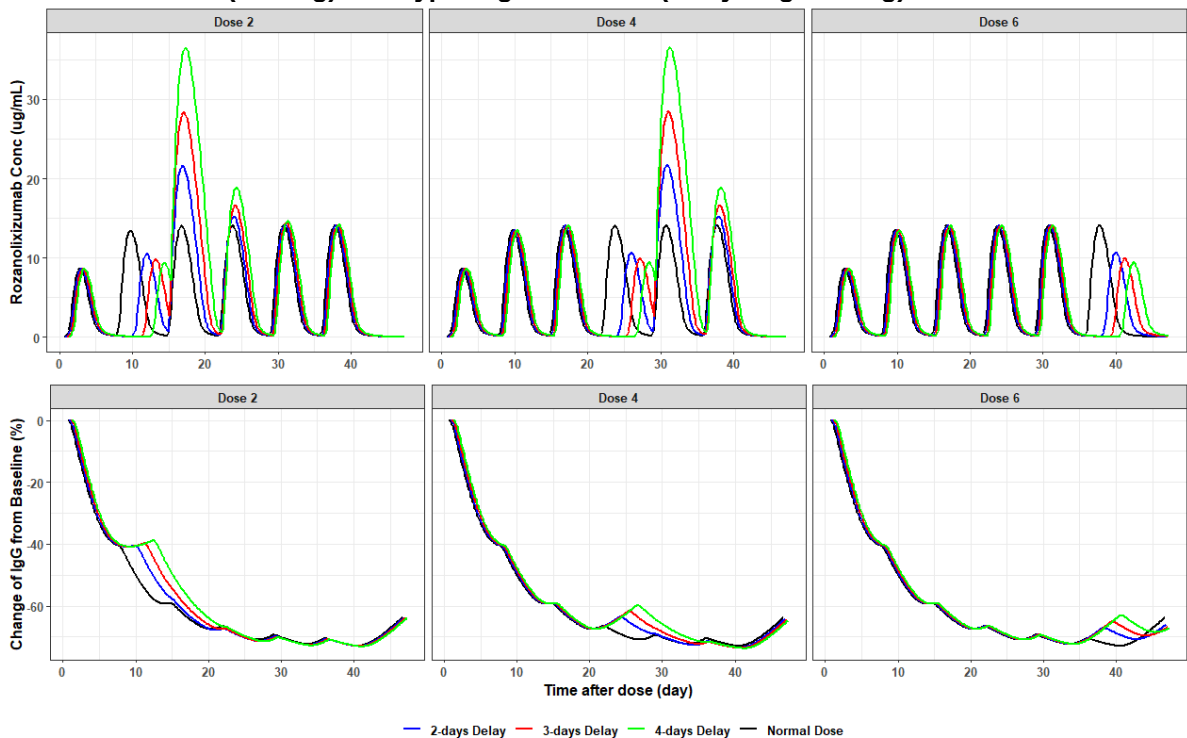
Source: Reviewer's Analysis

Evaluation of Proposed Dose Recommendation for Missed/Delayed Dose

The Applicant has proposed the following recommendation: "If a scheduled infusion is missed, rozanolixizumab may be administered up to 4 days after the scheduled time point. Thereafter,

resume the original dosing schedule until the treatment cycle is completed." To assess the validity of this treatment strategy after a delayed dose, the reviewer conducted PK/PD simulations. The simulation results indicate that a delayed dose of up to 4 days would not lead to a significant loss in maximum total IgG reduction, with a difference of approximately 1% observed ([Figure 36](#)).

Figure 36. PK/PD Simulation of Delayed Dose Scenarios for 6 Weekly SC Infusion of Rozanolixizumab (560 mg) in a Typical gMG Patient (Bodyweight:80 kg)



Source: Reviewer's analysis
Note: Solid lines represent medians of the predicted values.
Abbreviations: conc, concentration; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous

14.5.2.4. Listing of Analyses Codes and Output Files

Table 92. Listing of Analysis Codes and Output Files		
File Name	Description	Description
pk_analysis_Rozanolixizumab.R	Exploratory PK analysis	/BLA761286/Rozanolixizumab/PPK/Reviewer/Rscript/pk_analysis_Rozanolixizumab.R
Mg_Sim.R	PopPK/PD simulation	BLA 761286 Rozanolixizumab/PPK/Reviewer/Sim/MG_Sim/Mg_Sim.R

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

14.6. Pharmacogenetics

Not applicable.

15. Study Design, MG0004 and MG0007

Design, Study MG0004

Study MG0004 was a 52-week, open-label extension (OLE) study of MG0003. This study was replaced by MG0007.

Objectives

Primary Objective, Study MG0004

To evaluate the long-term safety and tolerability of rozanolixizumab in subjects with gMG who have moderate to severe symptoms and are seropositive for anti-AChR or anti-MuSK antibodies.

Primary Endpoints, Study MG0004

- Occurrence of treatment-emergent adverse event (TEAEs)
- Occurrence of TEAEs leading to permanent withdrawal of study drug
- Other safety endpoints included:
- Adverse events of special monitoring (severe headache, severe gastrointestinal (GI) disorders and opportunistic infections)
- Vital signs values and change from baseline
- 12-lead electrocardiogram values and change from baseline
- Clinical laboratory parameters (hematology, biochemistry, and urinalysis).

Secondary Objective, Study MG0004

To evaluate the long-term efficacy of rozanolixizumab in subjects with gMG who have moderate to severe symptoms and are seropositive for anti-AChR or anti-MuSK antibodies

Secondary Endpoints, Study MG0004

- Change from baseline at each scheduled assessment during treatment and observation periods in MG-ADL, myasthenia gravis composite (MG-C) score, quantitative myasthenia gravis (QMG), and use of rescue medication.

Eligibility Criteria

- Subjects must have completed the observation period in Study MG0003
- Subjects who discontinued study drug in MG0003 for reasons other than requiring rescue medication were not eligible for Study MG0004.
- Subjects who required IVIg or PEX rescue medication in the MG0003 observation period were not eligible for Study MG0004.

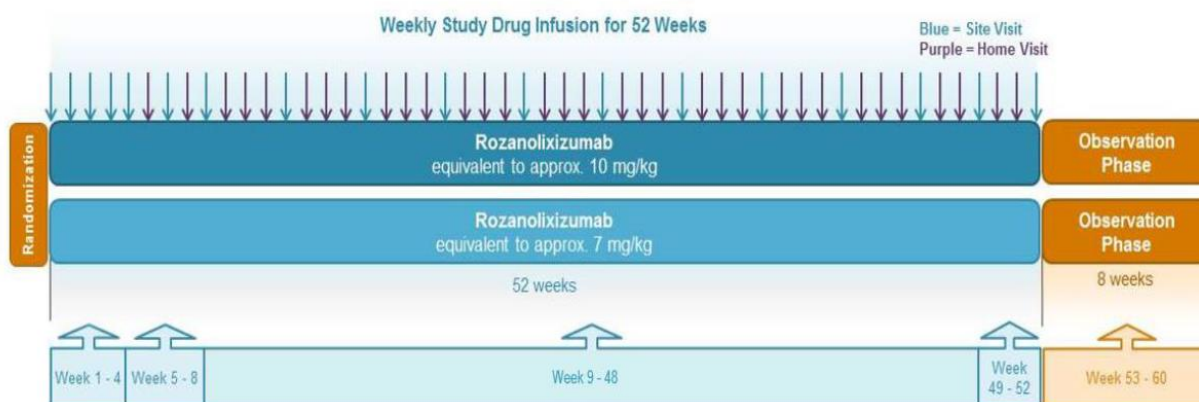
Basic Study Design, Study MG0004

Study MG0004 was a phase 3, multicenter, randomized, open-label extension (OLE) study with a weekly rozanolixizumab SC dosing regimen for 52 weeks either on site or at home followed by an 8-week observation period in adult subjects with gMG who completed the observation period in Study MG0003. Subjects were randomized 1:1 to receive rozanolixizumab either ≈ 7 mg/kg or ≈ 10 mg/kg dose based on body weight-tier similar to that in Study MG0003 (see Section 6.1).

Transition between Study MG0003 and Study MG0004: the final visit (visit 14) in Study MG0003 served as the first visit in MG0004.

Study MG0004 was replaced by MG0007, an OLE study with 6-week treatment cycles based on MG worsening. Subjects who completed a minimum of 6-week treatment in Study MG0004 were eligible to enroll in MG0007. An IDMC monitored the ongoing safety and efficacy of the Study.

Figure 37. Study Schematic



Source: MG0004 SAP September 23, 2021

Design, Study MG0007

Study MG0007 is an ongoing open label extension study to MG0003 and consists of repeated treatment cycles demanded by gMG worsening as defined in the protocol.

Objectives

Primary Objective, Study MG0007

To evaluate the safety and tolerability of 6-week treatment cycles with SC rozanolixizumab in subjects with gMG who have moderate to severe symptoms and are seropositive for anti-AChR or anti-MuSK antibodies

Primary Endpoints, Study MG0007

- Occurrence of TEAEs
- Occurrence of TEAEs leading to permanent withdrawal of study drug

Other Safety Endpoints, Study MG0007

- Occurrence of serious TEAEs
- Occurrence of TEAEs of special monitoring
- Vital signs values and change from baseline (blood pressure and pulse)
- 12-lead electrocardiogram values and change from baseline
- Laboratory parameters and change from baseline (hematology, clinical chemistry, and urinalysis).

Secondary Objective, Study MG0007

To evaluate the efficacy of 6-week treatment cycles with SC rozanolixizumab in subjects with gMG who have moderate to severe symptoms and are seropositive for anti-AChR or anti-MuSK antibodies

Secondary Endpoints, Study MG0007

- For each of the first three 6-week treatment cycles, change from baseline to day 43 in one treatment cycle in MG-ADL, MG-C score, and QMG
- Time between consecutive treatment cycles

Eligibility Criteria

Key Inclusion Criteria

- Adults aged ≥ 18 years with gMG who are anti-AChR or anti-MuSK antibody positive
- Must meet one of the following criteria:
 - Completed the observation period in Study MG0003
 - Required but not received IVIg/PEX during the observation period of MG0003
 - completed at least 6 visits in MG0004
- Body weight ≥ 35 kg at baseline
- Subjects who discontinued study drug in MG0003 for reasons other than requiring rescue medication were not eligible for Study MG0004.
- Subjects who required IVIg or PEX rescue medication in the MG0003 observation period were not eligible for Study MG0004.

Basic Study Design, MG0007

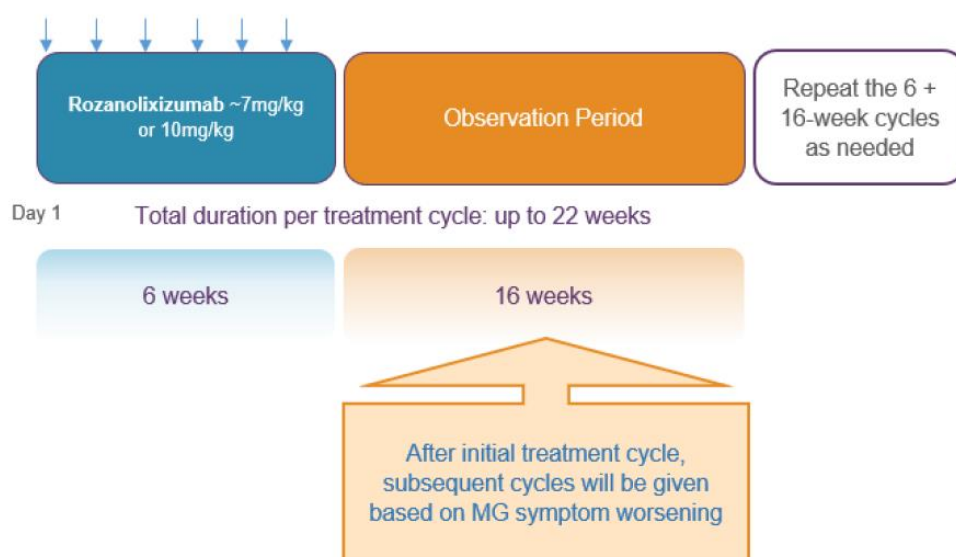
Study MG0007 is an ongoing phase 3, multicenter, randomized, open-label extension (OLE) study of MG0003 to evaluate 6-week treatment cycles of rozanolixizumab in subjects with gMG. An IDMC monitored the ongoing safety and efficacy of the study.

Subjects were randomized 1:1 to receive rozanolixizumab initial 6-week treatment cycle of either ≈ 7 mg/kg or ≈ 10 mg/kg dose based on body weight-tier similar to that in Study MG0003 followed by 16-weeks observation period (see Section 6.1, Figure 38).

Subjects are evaluated every 4 weeks. Subsequent 6-week treatment cycles are triggered in case of MG symptom worsening defined as an increase of 2 points on MG-ADL or 3 points on QMG scale between assessments, based on investigator's assessments.

The minimum time to start the next treatment cycle is 4 weeks following the last dose of the treatment period of the previous cycle. If a study participant requires treatment earlier than 4 weeks, IgG levels from the previous cycle are considered and discussed with the medical monitor. A new treatment cycle cannot be initiated until total IgG level is ≥ 2 g/L.

Figure 38. Study Design, MG0007



Source: Protocol Figure 1-2.

Abbreviations: MG, myasthenia gravis

Transition Between Study MG0003 and Study MG0007

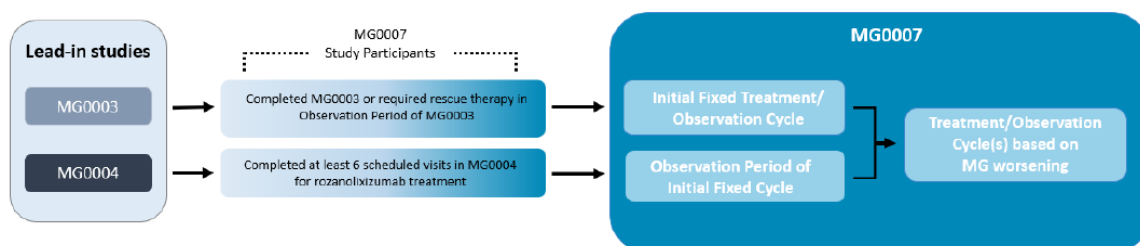
The rollover must be within 4 weeks after the end of study visit in MG0003 (Figure 39).

Transition Between Study MG0004 and MG0007

The rollover must be within 4 weeks after the premature end of treatment (at least six SC rozanolixizumab weekly dosing) or the end of study visit in MG0004 (Figure 39).

In case of more than four-week time interval from Study MG0003 or MG0004, a screening period of up to 4 weeks was applicable to confirm the eligibility for Study MG0007.

Figure 39. Entry Schema, Study MG0007



Source: Protocol Figure 1-1

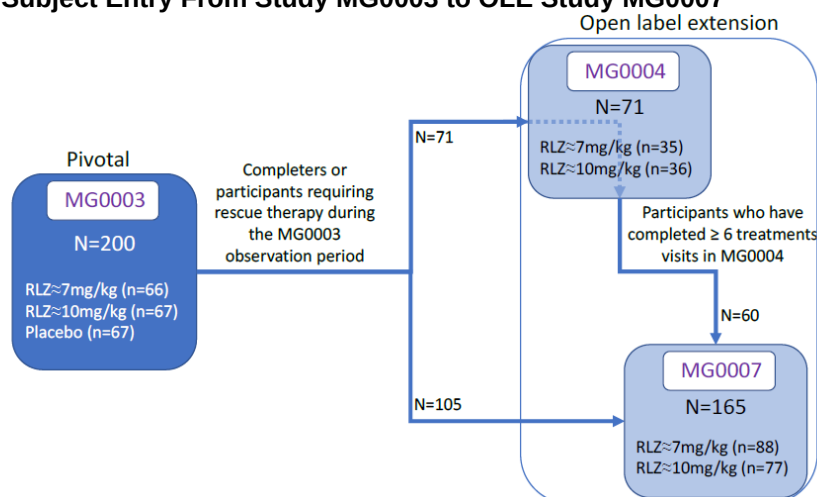
Note: subjects requiring rescue therapy and rolling over to OLE received rozanolixizumab and not IVIg/PEX

Abbreviations: IVIg, immunoglobulin; MG, myasthenia gravis; OLE, open-label extension; PEX, plasma exchange

Subject disposition through phase 3 studies is shown in [Figure 40](#).

Overall, a total of 165 subjects including 105 subjects from Study MG0003 and 60 subjects from Study MG0004 enrolled in the OLE Study MG0007. All of 165 subjects were enrolled during the coronavirus disease of 2019 (COVID-19) pandemic period. Of these, 88 subjects were assigned to rozanolixizumab ≈ 7 mg/kg group, and 77 subjects were assigned to rozanolixizumab ≈ 10 mg/kg group.

Figure 40. Subject Entry From Study MG0003 to OLE Study MG0007



Source: Module 2.2.5 Clinical Overview Figure 4-1 page 29.

Note: Participants requiring rescue therapy and rolling over to the open-label extensions did not receive IVIg/PLEX but rozanolixizumab.

Abbreviations: IVIg, immunoglobulin; MG, myasthenia gravis; OLE, open-label extension; PEX, plasma exchange;

RLZ, rozanolixizumab; $\approx$, approximate dose

Dose Modifications, Study MG0007

The dose adjustments to ≈ 7 mg/kg or ≈ 10 mg/kg were permitted at the beginning of each treatment cycle as per the investigator's discretion. Recommended dose modifications from ≈ 10 mg/kg to ≈ 7 mg/kg equivalent due to drug-related AEs included:

- Moderate to severe headaches
- Moderate to severe gastrointestinal disturbances
- Moderate to severe toxicities ($\geq$ grade 2 common terminology criteria for adverse events (CTCAE v5.0))
- Recurrent hypogammaglobulinaemia with a serum total IgG level of < 2 g/L

Use of Concomitant MG Care Medications, Study MG0007

The permitted concomitant medications are listed in [Table 93](#). The dose of all medications except steroids and acetylcholine esterase (AChE) inhibitors were maintained during the treatment cycle.

Table 93. Permitted Concomitant MG Care Medications, Study MG0007

Permitted Medications	Dose
Oral corticosteroids (eg, prednisolone)	No specific requirements
Methotrexate	≤ 30 mg/week
Mycophenolate mofetil	≤ 3 g/day
Cyclosporine ^a	≤ 5 mg/kg/day for unmodified ≤ 4 mg/kg/day for modified (microemulsion)
Azathioprine	≤ 3 mg/kg/day
Cholinesterase inhibitors	≤ 600 mg pyridostigmine/day
Tacrolimus ^b	≤ 5 mg/day

^a Doses higher than listed are permissible if trough level is ≤ 300 ng/mL.

^b If the total daily weight-based dose is > 5 mg, then a plasma trough level should be checked to ensure study participant is not above the recommended therapeutic range.

Source: Protocol [Table 6-3](#)

Abbreviations: MG, myasthenia gravis

Compliance With Good Clinical Practice, Studies MG0004, MG0007

Study execution, protocol adherence, and data integrity appear adequate. The data generated are interpretable. Union Chimique Belge (UCB), Inc. attested to good clinical practices such as human subject protection, institutional review board compliance, and clinical investigator obligations including financial disclosures as defined in International Council on Harmonisation-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

16. Efficacy

See Section [6.2.2.4.3](#) for the analyses and interpretation of efficacy.

APPEARS THIS WAY ON ORIGINAL

17. Clinical Safety

17.1. Safety Data Pool S1, Studies MG0003, MG0004, MG0007

Safety Pool S1 consists of all rozanolixizumab-treated subjects who have undergone at least one treatment cycle, defined as receiving at least one infusion of rozanolixizumab in any 6-week treatment period (See Section [7.4](#)).

For Safety Pool S1, the treatment-emergent adverse events were defined as:

- Study MG0003: Adverse event starting on or after the time of first rozanolixizumab administration up to and including 3 weeks (56 days) after the last dose in the treatment cycle.
- Study MG0004 (first 6 weeks of all subjects): Adverse event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab.
- Study MG0007: Adverse event starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle

17.1.1. Subject Disposition, Safety Pool S1

A total of 196 subjects were included in Safety Pool S1 and based on the maximum dose received in the first treatment cycle, 95 and 101 subjects were included in rozanolixizumab ≈ 7 mg/kg and ≈ 10 mg/kg dose groups, respectively. Out of 196 subjects in Safety Pool S1, 59 (30.1%) were permanently discontinued ([Table 94](#)). The most common reason for treatment discontinuation was occurrence of TEAEs in both rozanolixizumab dose groups. Another common reason for treatment discontinuation was withdrawal by subjects in the ≈ 10 mg/kg dose group.

Table 94. Subject Disposition and Reasons for Premature Treatment Discontinuation, Safety Pool S1, Study MG0003, MG0004, and MG0007

Disposition	RLZ $\approx$ 7mg/kg N=95 n (%)	RLZ $\approx$ 10mg/kg N=101 n (%)	RLZ Total N=196 n (%)
Permanently discontinued	23 (24.2)	36 (35.6)	59 (30.1)
Primary reason for discontinuation			
Adverse event	14 (14.7)	18 (17.8)	32 (16.3)
Lack of efficacy	2 (2.1)	1 (1.0)	3 (1.5)
Protocol violation	0	0	0
Lost to follow-up	2 (2.1)	0	2 (1.0)
Withdrawal by study participant	2 (2.1)	10 (9.9)	12 (6.1)
COVID-19 pandemic	0	1 (1.0)	1 (0.5)
Other	3 (3.2)	6 (5.9)	9 (4.6)

$\approx$ =approximate dose; COVID-19=coronavirus disease 2019; n=number of study participants; N=number of study participants randomized to the respective treatment group for their first RLZ cycle; RLZ=rozanolixizumab

Source: Module 2.7.4 Summary of Clinical Safety Section 1.2.4.2 Table 1-12 dated September 29, 2022

17.1.2. Baseline Characteristics, Safety Pool S1, Study MG0003, MG0004, and MG0007

Demographics for the pivotal placebo-controlled Study MG0003 are described in Section 6.2.2.4, based on the submitted data. Study MG0003 enrolled 200 subjects, almost all during the COVID-19 pandemic (n=183 [91.5%]; the pandemic start date March 20, 2020) and the rest (n=17 [8.5%]) during the pre-COVID-19 pandemic period. All 71 subjects in MG0004 entered from Study MG0003 and most (n=63 [88.7%]) subjects were enrolled during the COVID-19 pandemic. All 165 subjects including 105 subjects from Study MG0003 and 60 subjects from Study MG0004, entered Study MG0007 during the COVID-19 pandemic. The demographics for the Safety Pool S1 from these phase 3 studies are described in Table 95. One hundred seventeen (59.7%) were female. Subjects 65 years and older comprised 24.5% and subjects 75 years and older comprised 8.2% of total subjects. Subjects in the <50 kg body weight category at baseline were in low numbers (6.1%). Subjects with seropositivity for anti-AChR autoantibody and anti-MuSK autoantibody comprised 82.7% and 7.7%, respectively of total subjects when tested at baseline visit. A majority of subjects were Myasthenia Gravis Foundation of America (MGFA) disease Class IIIa followed by Class IIb and IIIb at baseline.

Table 95. Baseline Demographic and Clinical Characteristics, Safety Population, Study MG0003, MG0004, MG0007

Characteristic	Rozanolixizumab Total N=196
Sex, n (%)	
Female	117 (59.7)
Male	79 (40.3)
Age, years	
Mean (SD)	51.9 (16.3)
Median (min, max)	52 (18, 89)
Age group, years, n (%)	
≤18	1 (0.5)
19 to <65	147 (75.0)
≥65	48 (24.5)
Age group 2, years, n (%)	
≥75	16 (8.2)
Race, n (%)	
Asian	21 (10.7)
Black or African American	5 (2.6)
Native Hawaiian or other Pacific Islander	1 (0.5)
White	132 (67.3)
Missing	37 (18.9)
Ethnicity, n (%)	
Hispanic or Latino	12 (6.1)
Not Hispanic or Latino	150 (76.5)
Missing	34 (17.3)
Country of participation, n (%)	
Poland	27 (13.8)
United States	39 (19.9)
Others	130 (66.3)
Region of participation, n (%)	
Asia [excluding Japan]	7 (3.6)
Europe	118 (60.2)
Japan	13 (6.6)
North America	58 (29.6)
Is in United States, n (%)	
United States	39 (19.9)
Non-United States	157 (80.1)
Height (cm), n (%)	
Mean (SD)	169.9 (9.8)
Median (min, max)	170 (148.9, 198.1)

Characteristic	Rozanolixizumab Total N=196
Weight (kg), n (%)	
Mean (SD)	81.4 (24)
Median (min, max)	78 (37.7, 155.6)
Body weight category (kg), n (%)	
<50	12 (6.1)
50 to <70	59 (30.1)
70 to <100	81 (41.3)
≥100	44 (22.4)
BMI (kg/m ²), n (%)	
Mean (SD)	27.8 (6.5)
Median (min, max)	27.2 (13.7, 47.6)
BMI category (kg/m ²), n (%)	
<18.5	9 (4.6)
18.5 to <25	65 (33.2)
25 to <30	51 (26.0)
≥30	71 (36.2)
MGFA disease class at baseline, n (%)	
Class IIa	37 (18.9)
Class IIb	41 (20.9)
Class IIIa	72 (36.7)
Class IIIb	39 (19.9)
Class IVa	7 (3.6)
Thymectomy, n (%)	
N	115 (58.7)
Y	81 (41.3)
Duration of disease (years), n (%)	
Mean (SD)	8.6 (8.9)
Median (min, max)	5.7 (0.1, 48.9)
Baseline AChR status, n (%)	
Negative	22 (11.2)
Positive	162 (82.7)
Unknown	12 (6.1)
Baseline MuSK status, n (%)	
Negative	170 (86.7)
Positive	15 (7.7)
Unknown	11 (5.6)

Source: adsl.xpt; Software: R

Abbreviations: AChR, acetylcholine receptor; BMI, body mass index; MGFA, myasthenia gravis foundation of America; MuSK, muscle-specific tyrosine kinase; N, number of patients in treatment group; n, number of patients with given characteristic; RLZ, rozanolixizumab

Reviewer's Comments: Overall, the baseline characteristics of subjects in the Safety Pool S1 is consistent with the demographics of subjects in Study MG0003. The sex imbalance favoring females is consistent with the natural history of the disease, as described in Section 2. The relative proportion of anti-AChR-gMG and anti-MuSK-gMG in the Safety Pool S1 is consistent with the disease prevalence in the intended patient population (Gilhus et al. 2019). There are fewer subjects in the <50 kg body weight category similar to that in Study MG0003 and this may potentially impact the labeling for dosing in this particular group.

Impact of the COVID-19 Pandemic on Safety Pool S1, Studies MG0003, MG0004, MG0007

The impact of the COVID-19 pandemic was minor and affected a relatively small number of the subjects. A majority of the subjects (91.5% in MG0003, 88.7% in MG0004 and 100% in MG0007) enrolled were randomized during the COVID-19 pandemic (the first laboratory-confirmed case of COVID-19 in the United States was January 20, 2020; the WHO declared a pandemic on March 11, 2020). The pandemic impact on Study MG0003 is described in Section 6.2.2.4.1. There were no protocol deviations related to COVID-19 in Study MG0004. The pandemic impacted six (3.6%) subjects and a total of 11 visits including 8 visits due to confirmed COVID-19 infection (all visits not done) in Study MG0007.

Protocol Deviations, Safety Pool S1, Studies MG0003, MG0004, MG0007

No subjects were excluded from any analysis due to protocol deviation. Protocol deviations for MG0003 are described in Section 6.2.2.4.1. A total of 18 (10.9%) subjects had an important protocol deviation in Study MG0007 including, exclusion criteria deviation (n=10 [6.1%]), procedural noncompliance (n=3 [1.8%]), withdrawal criteria deviation and treatment noncompliance (n=2 [1.2%] each), and incorrect treatment dose (n=1 [0.6%]). A total of five (7%) subjects had an important protocol deviation due to procedural noncompliance in Study MG0004.

Reviewer's Comments: The protocol deviations affected 11% and 7% of the randomized subjects in Studies MG0007 and MG0004, respectively and none were excluded from any analysis. They were unlikely to have had an impact on the efficacy and safety analyses.

17.2. Overview of Treatment-Emergent Adverse Events Summary, Safety Pool S1, Studies MG0003, MG0004, MG0007

Table 96 shows a summary of treatment-emergent adverse events (TEAEs) in 196 subjects pooled in Safety Pool S1 from the Studies MG0003, MG0004, and MG0007. Of 196 subjects, 182 (92.9%) subjects experienced a TEAE with rozanolixizumab treatment. A majority (64.3%) of subjects had mild to moderately severe TEAEs. Serious adverse events occurred in 21.9% of the subjects. Rozanolixizumab was permanently discontinued in 14.8% of subjects due to TEAEs.

Table 96. Overview of Adverse Events, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

Event Category	RLZ Total N=196 n (%)
SAE	43 (21.9)
SAEs with fatal outcome	3 (1.5)
Life-threatening SAEs	1 (0.5)
AE leading to permanent discontinuation of study drug	29 (14.8)
AE leading to dose modification of study drug	44 (22.4)
AE leading to interruption of study drug	43 (21.9)
AE leading to reduction of study drug	1 (0.5)
AE leading to dose delay of study drug	0
Other	0
Any AE	182 (92.9)
Severe and worse	56 (28.6)
Moderate	80 (40.8)
Mild	46 (23.5)

Source: адае.хрt; Software: R

Treatment-emergent adverse events defined in the three studies a: MG0003 - as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004 - as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007 - defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004 - first 6 weeks of all study subjects, MG0007 - is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; RLZ, rozanolixizumab SAE, serious adverse event

17.3. Deaths in the Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, and MG0007

A total of five deaths were reported in the OLE Study MG0007 ([Table 97](#)). There were no new deaths reported in 120-day safety update dated February 3, 2023. Three deaths occurred in the setting of infection. Two deaths were attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pneumonia in unvaccinated individuals. One case of multilobar pneumonia in which no pathogen was identified. A role for rozanolixizumab in the TEAEs of COVID-19 and pneumonia cannot be ruled out. The reviewer notes that pneumonia is the most common of all infections in gMG patients with gMG and occurs due to bulbar and swallowing muscle weakness and immunocompromised status ([Prior et al. 2018](#); [Kassardjian et al. 2020](#)). Two deaths attributed to cardiac events occurred during follow-up period and before treatment in Study MG0007. Given the time to onset and the presence of medical comorbidities, these events were considered unrelated to rozanolixizumab.

The mortality rate observed in the Safety Pool S1 from Studies MG0003, MG0004, and MG0007 was 25.9 deaths per 1000 (5 deaths/193.05 person-years) and is similar to the mortality rate observed in pooled safety population for efgartigimod (30.5 deaths per 1000 subjects; Integrated Review.BLA761195.December 17, 2021).

Table 97. Treatment-Emergent Deaths in the Subjects Treated With Rozanolixizumab, Safety Population, Pool S1, Study MG0003, MG0004, MG0007

TEAE MedDRA v24	MG0007 RLZ Treatment at Time of Death	Days Since First Infusion ¹	Days Since Most Recent Infusion	Comment
COVID-19 (TEAE)	Cycle 1≈10 mg/kg Treatment Period	103 days	5 days	43-year-old female with severe COVID-19 infection was hospitalized and died 18 days after the first dose (her last dose) of RLZ in MG0007. The subject had received 6 doses of RLZ ≈10 mg/kg SC in MG0003. Not vaccinated for SARS-CoV2. A role of rozanolixizumab cannot be ruled out.
COVID-19 pneumonia (TEAE) Respiratory failure (TEAE)	Cycle 3 ≈ 10 mg/kg Treatment Period	145 days	2 days	55-year-old male with severe COVID-19 infection and respiratory failure was hospitalized, intubated and later had a tracheostomy. The subject died 26 days after the final 16 th RLZ infusion in MG0007. Treated with IVIg. The subject had received Placebo in MG0003. Risk factors included chronic lung disease, obesity, corticosteroids, and hypertension. Not vaccinated for SARS-CoV2. A role of rozanolixizumab cannot be ruled out.
Pneumonia (TEAE), and acute kidney failure, acute respiratory failure, cardiac failure, ARDS (non-TEAE)	Cycle 2 ≈ 7 mg/kg Follow-up Period	210 days	57 days	69-year-old male with diabetes, atrial fibrillation was hospitalized due to multifocal pneumonia and respiratory failure leading to acute renal and heart failure. SARS-CoV2 negative. The subject died 85 days after the final 10 th RLZ SC infusion in MG0007. The subject had received Placebo in MG0003. The subject was vaccinated for SARS-CoV2. Pneumonia was likely related to RLZ as serum IgG were not recovered and no pathogens were identified.

TEAE MedDRA v24	MG0007 RLZ Treatment at Time of Death	Days Since First Infusion ¹	Days Since Most Recent Infusion	Comment
Myocardial Infarction (non-TEAE)	Intermittent period ²	428 days	326 days	60-year-old male with diabetes and morbid obesity withdrew from the study due to lack of efficacy. Died from acute MI 326 days after last dose. The subject received all 6 RLZ 10 mg/kg SC doses in MG0003 and died 326 days after the final ≈15 weekly RLZ 10 mg/kg doses in MG0004. The subject enrolled into MG0007 but withdrew before any treatment due to lack of efficacy. Unrelated to RLZ.
Circulatory failure (TEAE) (after data cutoff July 8, 2022)	≈10 mg/kg Follow-up Period	478 days	51 days	81-year-old with poorly controlled diabetes, myocardial infarction, arrhythmia, hyperlipidemia, and aortic aneurysm was hospitalized for chest pain and dyspnea and died from “circulatory arrest” 51 days after the last dose 4 weeks into treatment cycle 6 in MG0007. The subject was withdrawn from MG0007 after 31 SC RLZ doses due to infective endocarditis. Tested positive for SARS-CoV2 infection. The subject received 5 doses of RLZ ≈10 mg/kg in MG0003, 007). Unrelated to RLZ.

Source: Module 2.7.4 Summary of Clinical Safety Table 2-8; mg0007-narratives; mg0007-report-body additional narratives

¹ the number of days between the first RLZ infusion in MG0003 and the event onset date +1 day

² A pretreatment MG0007 event that occurred 7 months after the final and ≈15 weekly doses in MG0004

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease of 2019, MedDRA, Medical Dictionary for Regulatory Activities; IVIg, immunoglobulin; RLZ, rozanolixizumab; SARS-CoV2, severe acute respiratory syndrome 2; SC, subcutaneous; TEAE, treatment-emergent adverse event

17.4. Serious Adverse Events in the Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, and MG0007

In Safety Pool S1, a total of 43 (21.9%) subjects experienced serious adverse events (SAEs) on rozanolixizumab treatment ([Table 98](#)). As occurred in the double-blind, placebo-controlled treatment period, the most common SAE was MG worsening and crisis (n=16 [8.1%]). Other SAEs with frequency >2 subjects included infections (4.1%) including COVID-19 (2%) and aseptic meningitis (0.5%), gastrointestinal disorders (2.6%), and neoplasms (1.5%).

MG Crisis

[Table 99](#) summarizes four subjects who experienced MG crisis on rozanolixizumab treatment in Study MG0007. All subjects were receiving rozanolixizumab ≈ 10 mg/kg dose treatment cycles. Three subjects were withdrawn from the study due to MG crisis and the use of rescue therapy. The precipitating event for MG crisis was not known in these subjects. In the fourth subject food impaction in esophagus resulted in severe dysphagia and MG crisis which resolved after the food bolus was removed endoscopically and the subject continued rozanolixizumab treatment according to the study design. None of the subjects in Studies MG0003 and MG0004 experienced MG crisis while receiving rozanolixizumab.

Worsening of Myasthenia Gravis

[Table 92](#) summarizes 12 subjects who experienced MG worsening on rozanolixizumab treatment in Safety Pool S1. Three out of 12 subjects experienced MG symptom worsening during the double-blind, placebo-controlled treatment in Study MG0003 and are described in [Section 7.6.2.3](#). The other nine subjects experienced MG worsening and their symptoms resolved during Study MG0007. Six out of nine subjects were withdrawn from Study MG0007 including five subjects due to MG worsening and one subject due to positive interferon gamma release assay (IGRA) on study entry. Five out of nine subjects required rescue therapy (IVIg or PEX). Two subjects had multiple episodes of MG worsening during Study MG0007. The triggering factors for MG worsening determined as per the investigator were SARS-CoV-2 vaccine (n=1), missing of doses due to exposure to COVID-19 positive person (n=1), and hypogammaglobulinemia (n=1).

Headache

Subject ID MG0003/ (b) (6) experienced serious headache after the second rozanolixizumab ≈ 10 mg/kg infusion in Study MG0003. The SAE is described in [Section 7.6.2.3](#). The event was likely related to rozanolixizumab.

Seizure

The SAE occurred in subject MG0003/ (b) (6) who was randomized to rozanolixizumab ≈ 7 mg/kg treatment group during Study MG0003. The event is described in [Section 7.6.2.3](#).

Transient Global Amnesia

Subject MG0007/ (b) (6) experienced the SAE 261 days after the first and seventh day after the most recent rozanolixizumab ≈ 10 mg/kg infusions in MG0007. At the time of the SAE, the subject had received five rozanolixizumab ≈ 10 mg/kg infusions in Study MG0003 followed by 23 rozanolixizumab ≈ 10 mg/kg infusions in Study MG0007. The SAE symptoms included dizziness, tinnitus, and disorientation in time and space. The brain imaging and electroencephalogram were without any fresh ischemic changes and seizure activity, respectively. The study drug dose was not changed, and the event was considered resolved 7 days after the symptom onset. The subject had multiple risk factors such as cardiac arrhythmia, myocardial infraction, hypertension, and diabetes. The transient global amnesia was considered severe. The event was unlikely related to rozanolixizumab.

COVID-19 Infection

Four subjects experienced the SAE of COVID-19 infection while receiving rozanolixizumab in Study MG0007 and a role of rozanolixizumab in the TEAE cannot be ruled out.

- Subject MG0007/ (b) (6) died due to COVID-19 infection after receiving the first infusion of rozanolixizumab ≈ 10 mg/kg dose in Study MG0007. The subject was not vaccinated for SARS-CoV2. The subject had completed the 6-week treatment cycle of rozanolixizumab in Study MG0003.
- Subject MG0007/ (b) (6) died due to COVID-19 pneumonia and respiratory failure after receiving 16 rozanolixizumab ≈ 10 mg/kg doses in Study MG0007. The subject was not vaccinated for SARS-CoV2.
- Subject MG0007/ (b) (6) was hospitalized for 3 days due to COVID-19 infection 37 days after the most recent rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. The dosing regimen for rozanolixizumab was unchanged. The subject had completed the 6-week treatment cycle of rozanolixizumab in Study MG0003.
- Subject MG0007/ (b) (6) was hospitalized for worsening COVID-19 infection after the first dose of rozanolixizumab ≈ 7 mg/kg in Study MG0007. The SAE resolved in 8 days after onset. This subject received placebo in Study MG0003. The study drug was interrupted due to COVID-19 infection. The subject continued in the study.

Other Serious Infections

- Subject MG0007/ (b) (6) experienced SAE of appendicitis complicated by cholecystitis, peritonitis, and liver abscess 38 days after the 18th infusion of rozanolixizumab ≈ 7 mg/kg in Study MG0007. The subject was withdrawn from the study due to infection requiring hospitalization.
- Subject MG0007/ (b) (6) experienced SAE of E. coli urosepsis 61 days after the first and 26 days after the most recent rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. The subject was withdrawn from the study due to infection requiring hospitalization. The infection resolved in 9 days after onset.

Aseptic Meningitis

Subject MG0007/ (b) (6) experienced an SAE of aseptic meningitis 36 hours after the first rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. The subject received placebo in Study MG0003. The subject reported severe headache with a numerical rating scale 9/10, stiff neck, diarrhea, nausea, and vomiting associated with fevers 38.4°C. In the emergency room, she received ceftriaxone, acyclovir, and dexamethasone for a presumed diagnosis of meningitis. CT head was reported as normal. A lumbar puncture showed 509 cells/ μ L (normal range: <5 cells/ μ L); mostly monocytes and granulocytes; glucose quotient slightly reduced; and proteins were normal. Multiplex polymerase chain reaction from cerebrospinal fluid (CSF) was negative for *Escherichia coli*, *Neisseria meningitidis*, *Haemophilus influenza*, *Listeria monocytogenes*, *Streptococcus agalactiae/pneumonia*, *cytomegalovirus*, *enterovirus*, *herpes simplex virus 1/2*, *varicella zoster virus*, *human herpesvirus 6*, *parechovirus*, and *cryptococcus neoformans/gattii*. The results for three COVID-19 tests, influenza test, tick-borne encephalitis,

Borrelia, and Epstein-Barr virus were negative. The subject was hospitalized. Laboratory test results for tuberculosis, Aspergillus antigen in CSF, and human immunodeficiency virus test were negative. A magnetic resonance imaging scan of the head showed meningeal enhancement in frontal ventricular system and around third ventricle. Her condition was diagnosed as aseptic meningitis. The headache improved to 4 out of 10, 2 days after onset. Antibiotic and antiviral therapy were stopped. The headaches resolved 5 days after onset and the subject was discharged from the hospital. The study drug was withdrawn due to aseptic meningitis and the subject discontinued from the study. The SAE was considered severe and related to rozanolixizumab.

There have been 2 additional cases of aseptic meningitis in studies evaluating rozanolixizumab for the treatment of myelin oligodendrocyte glycoprotein antibody disease (MOG-AD) (Module 2.7.4. Summary of Clinical Safety; see Section 7.7.1). These subjects received rozanolixizumab 560 mg or placebo. Both subjects developed symptoms 2 days after the first infusion and recovered 6 days and 12 days after onset, respectively. The pathophysiology of drug induced aseptic meningitis is not understood.

Acute Respiratory Failure

The SAE occurred in subject MG0003/ (b) (6) who was randomized to rozanolixizumab ≈ 10 mg/kg treatment during Study MG0003 in the setting of tracheal device dislocation and is described in Section 7.6.2.3.

Gastrointestinal Disorders

- Subject MG0007/ (b) (6) experienced hematochezia and abdominal pain and SAE large intestinal polyp 133 days after the first and 21 days after the most recent rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. She received placebo in Study MG0003. The subject was hospitalized, and the polyp was excised endoscopically. The pathology showed a low-grade tubular adenoma and high-grade tubulovillous adenoma. The study drug dose was not changed. The SAE of large intestinal polyp was unlikely related to rozanolixizumab given the time to onset, relatively short exposure to rozanolixizumab (12 weeks), and a prior history of positive occult blood test before the study entry.
- Subject MG0007/ (b) (6) experienced SAE of MG crisis and esophageal food impaction (see MG crisis above). The SAE of esophageal food impaction due to a meat bolus likely caused MG crisis and these events were unlikely related to rozanolixizumab.
- Subject MG0007/ (b) (6) experienced SAE of duodenal ulcer bleeding 3 days after receiving five SC infusions of rozanolixizumab ≈ 10 mg/kg dose in Study MG0007. The subject reported vomiting 10 to 11 times per day and diarrhea 9 to 10 times per day. The subject was hospitalized due to dehydration and electrolyte abnormalities. The symptoms resolved nine days after onset. The study drug dose was reduced to ≈ 7 mg/kg due to the SAE. The SAE of duodenal ulcer bleeding was unlikely related to rozanolixizumab because the subject had a previous history of gastric ulcer perforation, duodenal stenosis, and a silent duodenal ulcer. A potential role of rozanolixizumab in the events of vomiting and diarrhea cannot be ruled out given the frequency of these events in the subjects treated with rozanolixizumab in the study, the suggestive time to onset and a positive rechallenge (the subject had experienced moderate diarrhea on the day of the first infusion).

Other gastrointestinal SAEs included gastritis and vomiting in one subject each receiving rozanolixizumab $\approx$ 7 mg/kg infusion during Study MG0003.

Neoplasms

- Subject MG0007/ (b) (6) experienced SAE of retroperitoneal neoplasm and thymoma, and adrenal disorder 263 days after the first and fourth day after the most recent rozanolixizumab $\approx$ 7 mg/kg infusion in Study MG0007. The subject had received a total of seven infusions in Study MG0007. The subject was randomized to placebo in Study MG0003. A CT scan showed abnormalities suggestive of two moderate thymomas, moderate focal lesion in the left kidney and adrenal gland, and moderate neoplastic infiltrations in retroperitoneal space. The study drug was withdrawn due to SAE and the subject discontinued from the study. Thymoma is a known association of gMG. The SAEs of a lesion in the left kidney and adrenal gland and retroperitoneal neoplasm were unlikely related to rozanolixizumab
- Subject MG0007/ (b) (6) experienced SAE of invasive ductal breast carcinoma before the first dose of rozanolixizumab in Study MG0007. The subject was randomized to placebo in Study MG0003. The study drug was withdrawn. The SAE was unlikely related to rozanolixizumab.
- Subject ID MG0003/ (b) (6) experienced oral herpes, metastatic squamous cell carcinoma in the inguinal region and femoral vein thrombosis 26 days after the first and fourth day after the fourth rozanolixizumab $\approx$ 10 mg/kg SC infusion in Study MG0003 that led to treatment discontinuation. The SAE was unlikely related to rozanolixizumab because the subject had episodes of squamous cell carcinoma before enrolling into Study MG0003 and a relatively short duration of exposure to rozanolixizumab (4 weeks).

Pericarditis

- Subject MG0004/ (b) (6) experienced SAE of moderately severe pericarditis 4 days after three infusions of rozanolixizumab $\approx$ 10 mg/kg in Study MG0004. The subject had received six infusions of rozanolixizumab $\approx$ 7 mg/kg in Study MG0003. Pericarditis was diagnosed based on echocardiogram and elevated C-reactive protein. The episode resolved in 6 days after onset. The study drug was interrupted due to SAE. The subject completed six infusions in MG0004 and rolled into Study MG0007. The subject had no prior history of cardiac disease. A potential role of rozanolixizumab in the SAE of pericarditis cannot be ruled out.

Myocardial Infarction

- Subject MG0007/ (b) (6) experienced SAE of myocardial infarction 55 days after the most recent infusion of rozanolixizumab ≈ 10 mg/kg in Study MG0007. The subject had cardiac risk factors such as hypertension, obesity, and a prior history of renal stent placement. The event was considered resolved on the same day after angioplasty and three stent placements. The study drug dose was considered interrupted due to SAE. The study drug dose was unchanged and the subject continued receiving rozanolixizumab in Study MG0007. The SAE of myocardial infarction was unlikely related to rozanolixizumab because the time to onset for the event was less suggestive and the subject had alternative etiologies of medical comorbidities.

Table 98. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in the Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

System Organ Class Preferred Term	RLZ Total N=196 n (%)
Any SAE	43 (21.9)
Nervous system disorders (SOC)	19 (9.7)
Myasthenia gravis	12 (6.1)
Myasthenia gravis crisis	4 (2.0)
Headache	1 (0.5)
Seizure	1 (0.5)
Transient global amnesia	1 (0.5)
Infections and infestations (SOC)	8 (4.1)
COVID-19	3 (1.5)
Complicated appendicitis	1 (0.5)
COVID-19 pneumonia	1 (0.5)
Liver abscess	1 (0.5)
Meningitis aseptic	1 (0.5)
Pneumonia	1 (0.5)
Urosepsis	1 (0.5)
Gastrointestinal disorders (SOC)	5 (2.6)
Duodenal ulcer hemorrhage	1 (0.5)
Gastritis	1 (0.5)
Large intestine polyp	1 (0.5)
Esophageal food impaction	1 (0.5)
Vomiting	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	3 (1.5)
Invasive ductal breast carcinoma	1 (0.5)
Metastatic squamous cell carcinoma	1 (0.5)
Retroperitoneal neoplasm	1 (0.5)
Thymoma	1 (0.5)
Cardiac disorders (SOC)	2 (1.0)
Myocardial infarction	1 (0.5)
Pericarditis	1 (0.5)
Musculoskeletal and connective tissue disorders (SOC)	2 (1.0)
Arthralgia	1 (0.5)
Osteoarthritis	1 (0.5)

System Organ Class	RLZ Total
Preferred Term	N=196
	n (%)
Renal and urinary disorders (SOC)	2 (1.0)
Dysuria	1 (0.5)
Nephrolithiasis	1 (0.5)
Endocrine disorders (SOC)	1 (0.5)
Adrenal disorder	1 (0.5)
Eye disorders (SOC)	1 (0.5)
Macular hole	1 (0.5)
General disorders and administration site conditions (SOC)	1 (0.5)
Chest pain	1 (0.5)
Product issues (SOC)	1 (0.5)
Device dislocation	1 (0.5)
Reproductive system and breast disorders (SOC)	1 (0.5)
Cervical dysplasia	1 (0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.5)
Acute respiratory failure	1 (0.5)
Skin and subcutaneous tissue disorders (SOC)	1 (0.5)
Subacute cutaneous lupus erythematosus	1 (0.5)
Surgical and medical procedures (SOC)	1 (0.5)
Spinal operation	1 (0.5)

Source: adae.xpt; Software: R

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Treatment-emergent adverse events defined in the three studies as: MG0003 - as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004 - as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007 - defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004 - first 6 weeks of all study subjects, MG0007 - is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

Table 99. Treatment-Emergent Serious Adverse Event Myasthenia Gravis Crisis in the Subjects Treated With Rozanolixizumab: Safety Population, Pool S1, Studies MG0003, MG0004, MG0007 (n=4)

Subject ID	Study Arm RLZ Dose	Time Between Onset and First Infusion Days MG0003/ MG0004/ MG0007	Time Between Onset and Last Infusion Days MG0007	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0007- (b) (6)	≈10 mg/kg	317 / 219 / 114	20	9	Severe (unrelated)	Resolved. During the observation period after the 2 nd treatment cycle, food impaction in esophagus resulted in severe dysphagia and MG crisis. The food bolus was removed endoscopically. Received prednisone. No MG worsening on RLZ ≈10 mg/kg dose in Studies MG0003 (6 doses) and MG0004 (approximately 10 doses).
MG0007- (b) (6)	≈10 mg/kg	75 / N.A./ 19	19	Ongoing	Severe (unrelated)	Study drug withdrawn due to MG crisis (walking disability, dysarthria, generalized limb weakness and fatigue, neck flexor weakness) after the 1 st infusion in MG0007. Precipitating event for the crisis unknown. Missed 2 doses due to drug nonavailability at the site. Received IVIg, intubated and required tracheostomy and ventilatory assistance for respiratory distress. No MG worsening on RLZ ≈7 mg/kg 6 doses in Study MG0003.
MG0007- (b) (6)	≈10 mg/kg	N.A./ 72 / 2	2	63	Severe (unrelated)	Resolved. Study drug withdrawn due to MG crisis (dysphagia, dysarthria, dyspnea, weakness, diplopia). The event occurred 2 days after the 1 st infusion in MG0007. Received IVIg and PEX. Precipitating event for the crisis unknown. No MG worsening on placebo in Study MG0003 and 7 doses of RLZ ≈10 mg/kg dose in Study MG0004.

Subject ID	Study Arm RLZ Dose	MG0003/ MG0004/ MG0007	Time Between Onset and First Infusion Days	Time Between Onset and Last Infusion Days	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0007- (b) (6)	≈10 mg/kg		188 / N.A./ 64	23	22	Severe (unrelated)	Resolved. MG crisis (muscle weakness, tachypnea, cough) occurred in the first 4 weeks after the 1 st treatment cycle. Treated with diltiazem and PEX. Withdrawn from the study as the subject met withdrawal criteria (treated with PEX). Precipitating event for the crisis unknown. No MG worsening on RLZ ≈10 mg/kg dose in Study MG0003 (6 doses).

Source: Module 5.3.5.2 MG0007-narratives

Abbreviations: IVIg, intravenous immunoglobulin; MG, myasthenia gravis; N.A., not applicable.; PEX, plasma exchange; RLZ, rozanolixizumab

Table 100. Treatment-Emergent Serious Adverse Event Myasthenia Gravis Worsening in the Subjects Treated With Rozanolixizumab: Safety Population, Pool S1, Studies MG0003, MG0004, MG0007 (n=12)

Subject ID	Study Arm RLZ Dose	MedDRA PT	MG0003/ MG0004/ MG0007	Time Between Onset and First Infusion Days	Time Between Onset and Last Infusion Days	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0003/ (b) (6)	≈10 mg/kg	MG exacerbation	76 / N.A./ N.A.	39	9		Severe (unrelated)	Resolved. The MG worsening event (unspecified) occurred during the observation period after the sixth and last infusion in Study MG0003. Treated with IVIg. Discontinued the study during observation period due to MG worsening. Did not enroll into MG0004 or MG0007.
MG0003/ (b) (6)	≈10 mg/kg	MG worsening	53 / N.A./ N.A.	18	13		Severe (unrelated)	Resolved. The MG worsening event (ptosis, double vision, dysarthria, fatigue while chewing, muscle weakness) occurred during the observation period after the sixth and last infusion in Study MG0003. Treated with IVIg. Completed the Study MG0003. Did not enroll into MG0004 or MG0007.

Subject ID	Study Arm RLZ Dose	MedDRA PT	Time Between Onset and First Infusion Days MG0003/ MG0004/ MG0007	Time Between Onset and Last Infusion Days	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0003/ (b) (6)	≈7 mg/kg	MG exacerbation	3 / N.A./ N.A.	3	2	Severe (vomiting related to study drug)	Resolved. The MG worsening event (dysarthria, ptosis, and shortness of breath) occurred after the first infusion in Study MG0003. No rescue therapy. Treated for severe vomiting and aspiration pneumonia. No ventilation support. Unchanged pyridostigmine. Missed second dose of the study drug. Received five doses in the study. Enrolled into MG0007 OLE
MG0007- (b) (6)	≈10 mg/kg	MG worsening	N.A./ 353 / 218	1	14	Severe (unrelated)	Resolved. The MG worsening (unspecified) occurred on the day of the fifth Treatment cycle and at the end of the 4-week observation period in Study MG0007. Hospitalized for the event. Discharge details unknown. No changes in study treatment. Precipitating event for the MG symptom worsening unknown. No MG worsening on placebo in MG0003 and approximately 14 doses of RLZ ≈10 mg/kg in MG0004.
			N.A./ 101	1	4	Severe (unrelated)	Resolved. The MG worsening event (MGFA Class IVb; QMG 39; dysphagia, a feeling of lack of air) occurred on the same day as the most recent infusion (n=13 doses) in Study MG0007. Treated with methylprednisolone in a hospital. Triggering factor as per the investigator was SARS-CoV-2 vaccine. No change in RLZ dose. No MG worsening on placebo in MG0003.
			N.A./ 255	10	5	Severe (unrelated)	Resolved. The MG worsening event (increase generalized weakness and respiratory disorders) occurred during the observation period after the 5 th treatment cycle in which one dose was missed (total 26 doses of RLZ) in Study MG0007. Treated with methylprednisolone and azathioprine in a hospital. No change in RLZ dose.
MG0007- (b) (6)	≈7 mg/kg	MG worsening	N.A./ 266	21	5	Severe (unrelated)	Resolved. the MG worsening event (weakness of the mimic, masticatory and respiratory muscles) occurred during the same observation period as the previous event. No change in RLZ dose. Symptoms recovered during RLZ treatment cycle.

Subject ID	Study Arm RLZ Dose	MedDRA PT	Time Between Onset and First Infusion Days MG0003/ MG0004/ MG0007	Time Between Onset and Last Infusion Days	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0007- (b) (6)	≈10 mg/kg	MG worsening	559 / 496 / 279	13	32	Severe (unrelated)	Resolved. Study drug withdrawn due to MG worsening. The event (dyspnea) occurred during the observation period after the 4 th treatment cycle in Study MG0007. Required intubation and IVIg and methylprednisolone treatment. As per the investigator, a possible trigger was skipping the study drug twice due to close contact with COVID-19 positive person. No MG worsening on RLZ 7 mg/kg 6 doses in MG0003 and approximately 19 doses in MG0004.
MG0007- (b) (6)	≈10 mg/kg	MG worsening	N.A./ 43	43	20	Severe (unrelated)	Resolved. The MG worsening (respiratory muscle weakness, right facio-brachio-crural weakness) occurred after the 1 st infusion in Study MG0007. Treated with PEX and noninvasive ventilation. The subject had a positive interferon gamma release assay on entry to MG0007. Quantiferon gold Plus TB test negative. Withdrawn from study after the 1 st infusion. No MG worsening on placebo in MG0003.
			288 / 191 / 53	17	5	Moderate (unrelated)	Resolved. The MG worsening event (visual, speech, and chewing difficulties) during the observation period after the 1 st treatment cycle (RLZ 6 doses) in Study MG0007. Treated with IVIg. No MG worsening on RLZ ≈7 mg/kg 5 doses in MG0003 and ≈10 mg/kg 17 doses in MG0004.
MG0007- (b) (6)	≈10 mg/kg	MG worsening	310 / 213 / 75 327 / 230 / 92	39	6	Moderate (unrelated)	Resolved. The MG worsening event (muscle weakness, double vision, dysphagia, and dyspnea) occurred during the same observation period as the previous event. Treated with IVIg and methylprednisolone.
				56	5	Moderate (unrelated)	Resolved. Study drug withdrawn due to MG worsening. The MG worsening event (unspecified) occurred during the same observation period as the previous event. Treated with IVIg.
MG0007- (b) (6)	≈7 mg/kg	MG aggravated	423 / 325 / 170	17	20	Severe (unrelated)	Resolved. The MG worsening event (dyspnea, dysphagia, dysarthria) occurred during the observation period after treatment cycle 3 in Study MG0007 and improved after restarting rozanolixizumab. No MG worsening on RLZ ≈10 mg/kg 6 doses in MG0003 and ≈7 mg/kg 10 doses in MG0004.

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Subject ID	Study Arm RLZ Dose	MedDRA PT	Time Between Onset and First Infusion Days MG0003/ MG0004/ MG0007	Time Between Onset and Last Infusion Days	Duration Days	Intensity (Relation to Study Drug)	Outcome
MG0007- (b) (6)	≈7 mg/kg	MG exacerbation	N.A./ 129 / 32	4	Unknown	Severe (unrelated)	Resolved. The MG worsening event (ophthalmoplegia and muscle weakness) occurred after the 5 th dose in the 1 st treatment cycle of Study MG0007. Treated with methylprednisolone. Study drug withdrawn due to MG worsening. No MG worsening on placebo in MG0003 and ≈7 mg/kg 8 doses in MG0004.
MG0007- (b) (6)	≈7 mg/kg	MG worsening	310 / N.A./ 186	25	6	Severe (unrelated)	Resolved. The MG worsening event (fatigue while chewing, choking, and exertional shortness of breath) occurred after 10 infusions in Study MG0007. As per the investigator, the triggering factor was hypogammaglobulinemia. Treated with IVIg. Study drug withdrawn due to MG worsening. No MG worsening on RLZ ≈10 mg/kg 6 doses in MG0003.
MG0007- (b) (6)	≈7 mg/kg	MG exacerbation	140 / N.A./ 41	7	19	Severe (unrelated)	Resolved. The MG worsening event (muscle weakness, hoarse voice, ptosis, difficulty holding head, fatigue while chewing, shortness of breath) after 6 infusions in Study MG0007. Treated with PEX. Study drug withdrawn due to MG worsening. No MG worsening on RLZ ≈7 mg/kg 6 doses in MG0003.

Source: Module 5.3.2.1. MG0003-narratives and Module 5.3.5.2 MG0007-narratives

Abbreviations: IVIg, intravenous immunoglobulin; MedDRA, Medical Dictionary for Regulatory Activities; MG, myasthenia gravis; N.A., not applicable.; PEX, plasma exchange; RLZ, rozanolixizumab; SARS-CoV2, severe acute respiratory syndrome 2

17.5. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation in the Subjects Treated with Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, and MG0007

In Safety Pool S1, a total of 29 (14.8%) subjects discontinued rozanolixizumab treatment due to adverse events ([Table 101](#)). The most common TEAEs leading to treatment discontinuation were MG worsening including crisis (n=7), infections (n=6), and aseptic meningitis (n=1). The brief case summaries of these subjects are described in the SAE section above. One subject discontinued treatment due to headache. Five subjects discontinued treatment due to abnormal investigations including blood immunoglobulin G decreased (n=2), Interferon gamma release assay positive (n=2), and liver function test increased (n=1).

Headache

Subject MG0003/ (b) (6) discontinued treatment after the first rozanolixizumab ≈ 7 mg/kg infusion in Study MG0003 due to severe headache. Four days after the first dose of rozanolixizumab treatment, the subject experienced pulsatile moderately severe headache, nausea, photophobia, phonophobia, and vertigo. She reported pyrexia (fevers; unspecified) during this event. The subject received ibuprofen and paracetamol. The event resolved 4 days after onset. There is no additional clinical information in the case narrative. Given the suggestive time to onset the adverse event (AE) of headache was likely related to rozanolixizumab.

Blood Immunoglobulin G Decreased

Two (1 percent) subjects MG0007/ (b) (6) and MG0007/ (b) (6) discontinued treatment due to hypogammaglobulinemia on rozanolixizumab ≈ 10 mg/kg and ≈ 7 mg/kg treatment, respectively in Study MG0007. The lowest IgG levels were <1.09 g/L and 1.81 g/L, respectively (normal reference: 7.57 to 19.41 g/L). No infections were reported during treatment cycles according to the available information in MG0007 case narratives. Serum IgG reductions are expected due to rozanolixizumab mechanism of action.

Interferon Gamma Release Assay (IGRA) Positive

Two (1%) subjects discontinued treatment due to IGRA test positive in Study MG0007. Subject MG0007/ (b) (6) received six infusions of rozanolixizumab ≈ 7 mg/kg dose level and tested IGRA positive from the blood sample taken during the last visit at 99 days in Study MG0003. At the time of the test result the subject had received the first rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. QuantiFERON Gold Plus tuberculosis test was positive. Clinical presentation and follow up for the tuberculosis were not described in the case narrative. A potential role of rozanolixizumab cannot be ruled out however, the reviewer notes that the subject resides in a country with a high risk of tuberculosis. Subject MG0007/ (b) (6) had a positive IGRA test

after the first rozanolixizumab ≈ 10 mg/kg infusion in Study MG0007. QuantiFERon Gold Plus tuberculosis (TB) was negative. The subject had received placebo in Study MG0003. The subject later developed MG worsening 43 days after the most recent rozanolixizumab infusion. The event of a positive IGRA test was unlikely related to rozanolixizumab because the subject received only one dose of rozanolixizumab and tested positive on study entry.

Abnormal Liver Function Tests

Subject MG0007/ (b) (6) discontinued treatment due to increased liver enzymes (aspartate aminotransferase [AST] 441 U/L [normal reference: 5 to 34 u/L], ALT 861 [normal reference: 0 to 55 u/L], lactate dehydrogenase 423 U/L [normal reference: 125 to 220 u/L]) which occurred after the first infusion of rozanolixizumab ≈ 10 mg/kg in Study MG0007 and was attributed to cholelithiasis (gall stones). Serum bilirubin and alkaline phosphatase levels remained within reference range. The subject received ursodeoxycholic acid as a treatment to dissolve gall stones and the TEAE resolved in 36 days after onset. The subject had received five infusions of rozanolixizumab ≈ 10 mg/kg in Study MG0003 without abnormalities in liver function tests. The TEAE of abnormal liver function was unlikely related to rozanolixizumab.

Table 101. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term in the Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

System Organ Class Preferred Term	RLZ Total N=196 n (%)
Any AE leading to discontinuation	29 (14.8)
Nervous system disorders (SOC)	8 (4.1)
Myasthenia gravis	5 (2.6)
Myasthenia gravis crisis	2 (1.0)
Headache	1 (0.5)
Infections and infestations (SOC)	7 (3.6)
Complicated appendicitis	1 (0.5)
COVID-19	1 (0.5)
COVID-19 pneumonia	1 (0.5)
Meningitis aseptic	1 (0.5)
Oral herpes	1 (0.5)
Pneumonia	1 (0.5)
Urosepsis	1 (0.5)
Investigations (SOC)	5 (2.6)
Blood immunoglobulin G decreased	2 (1.0)
Interferon gamma release assay positive	2 (1.0)
Liver function test increased	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	3 (1.5)
Invasive ductal breast carcinoma	1 (0.5)
Metastatic squamous cell carcinoma	1 (0.5)
Retroperitoneal neoplasm	1 (0.5)
Thymoma	1 (0.5)

System Organ Class Preferred Term	RLZ Total N=196 n (%)
Skin and subcutaneous tissue disorders (SOC)	2 (1.0)
Pruritus	1 (0.5)
Subacute cutaneous lupus erythematosus	1 (0.5)
Gastrointestinal disorders (SOC)	2 (1.0)
Abdominal pain upper	1 (0.5)
Diarrhea	1 (0.5)
Vomiting	1 (0.5)
Musculoskeletal and connective tissue disorders (SOC)	2 (1.0)
Arthralgia	1 (0.5)
Tendon disorder	1 (0.5)
Tenosynovitis	1 (0.5)
Endocrine disorders (SOC)	1 (0.5)
Adrenal disorder	1 (0.5)
Product issues (SOC)	1 (0.5)
Device dislocation	1 (0.5)
Vascular disorders (SOC)	1 (0.5)
Deep vein thrombosis	1 (0.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as: MG0003 - as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004 - as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007 - defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004 - first 6 weeks of all study subjects, MG0007 - is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab; SOC, system organ class

17.6. Treatment-Emergent Adverse Events, Safety Population, Safety Pool S1, Studies MG0003, MG0004, and MG0007

[Table 102](#) lists the TEAEs in the Safety Pool S1 with a cutoff frequency of at least 5% in the either dose of rozanolixizumab arm consistent with the cutoffs used labeling for efgartigimod, eculizumab, and ravulizumab, the monoclonal antibodies approved for the indication of anti-AChR antibody seropositive MG.

Overall, the incidence of most frequent TEAEs in the rozanolixizumab treated subjects in Safety Pool S1 was consistent with that observed during the double-blind placebo-controlled treatment cycle in Study MG0003. The most common system organ class with TEAEs $\geq 5\%$ frequency was nervous system disorders followed by infections, gastrointestinal disorders, general disorders, and administration site conditions ([Table 95](#)). The most frequently reported TEAEs were headache, infections including upper respiratory tract infections, diarrhea, pyrexia, injection site reactions, musculoskeletal pain, abdominal pain, and nausea. The most frequent abnormal

laboratory test results included decreased blood immunoglobulin levels. Serum IgG reductions are expected due to rozanolixizumab mechanism of action.

Relatively more subjects in the rozanolixizumab ≈ 10 mg/kg dose group reported infections compared to the ≈ 7 mg/kg dose group. The incidence of other TEAEs were balanced between the rozanolixizumab treatment arms.

Table 102. Treatment-Emergent Adverse Events Occurring at $\geq 5\%$ Frequency in the Subjects Treated With Rozanolixizumab, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

System Organ Class Grouped Query	RLZ≈ 7 mg/kg N=95 n (%)	RLZ≈ 10 mg/kg N=101 n (%)	RLZ Total N=196 n (%)
Any AE	89 (93.7)	93 (92.1)	182 (92.9)
Nervous system disorders (SOC)	61 (64.2)	59 (58.4)	120 (61.2)
Headache	52 (54.7)	46 (45.5)	98 (50.0)
Myasthenia gravis	10 (10.5)	12 (11.9)	22 (11.2)
Dizziness	5 (5.3)	7 (6.9)	12 (6.1)
Infections and infestations (SOC)	38 (40.0)	56 (55.4)	94 (48.0)
Upper respiratory tract infection	12 (12.6)	22 (21.8)	34 (17.3)
COVID-19	9 (9.5)	19 (18.8)	28 (14.3)
Urinary tract infection	8 (8.4)	9 (8.9)	17 (8.7)
Herpes simplex	1 (1.1)	10 (9.9)	11 (5.6)
Gastrointestinal disorders (SOC)	45 (47.4)	44 (43.6)	89 (45.4)
Diarrhea	30 (31.6)	32 (31.7)	62 (31.6)
Abdominal pain	14 (14.7)	16 (15.8)	30 (15.3)
Nausea	14 (14.7)	19 (18.8)	33 (16.8)
Vomiting	6 (6.3)	9 (8.9)	15 (7.7)
General disorders and administration site conditions (SOC)	40 (42.1)	47 (46.5)	87 (44.4)
Musculoskeletal pain	14 (14.7)	20 (19.8)	34 (17.3)
Pyrexia	16 (16.8)	22 (21.8)	38 (19.4)
Injection site reaction	14 (14.7)	18 (17.8)	32 (16.3)
Asthenia, fatigue, malaise	9 (9.5)	11 (10.9)	20 (10.2)
Musculoskeletal and connective tissue disorders (SOC)	29 (30.5)	35 (34.7)	64 (32.7)
Arthralgia	11 (11.6)	11 (10.9)	22 (11.2)
Myalgia	9 (9.5)	7 (6.9)	16 (8.2)

System Organ Class Grouped Query	RLZ≈7 mg/kg N=95 n (%)	RLZ≈10 mg/kg N=101 n (%)	RLZ Total N=196 n (%)
Investigations (SOC)	22 (23.2)	30 (29.7)	52 (26.5)
Blood immunoglobulin decreased	14 (14.7)	15 (14.9)	29 (14.8)
Lymphocyte count decreased	4 (4.2)	7 (6.9)	11 (5.6)
Skin and subcutaneous tissue disorders (SOC)	18 (18.9)	19 (18.8)	37 (18.9)
Rash	9 (9.5)	6 (5.9)	15 (7.7)
(Cardio) vascular disorders (SOC)	13 (13.7)	15 (14.9)	28 (14.3)
Hypertension	8 (8.4)	7 (6.9)	15 (7.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as: MG0003 - as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004 - as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007 - defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004 - first 6 weeks of all study subjects, MG0007 - is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

Abdominal pain contains: Abdominal discomfort, Abdominal pain, Abdominal pain upper, Abdominal distension, Abdominal pain lower, Flank pain

Arthralgia contains: Arthralgia, Arthritis

Asthenia, fatigue, malaise contains: Fatigue, Asthenia, Malaise

Blood immunoglobulin decreased contains: Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Hypoglobulinaemia, Blood immunoglobulin M decreased

COVID-19 contains: COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive

Diarrhea contains: Diarrhea, Frequent bowel movements

Dizziness contains: Vertigo, Dizziness

Headache contains: Headache, Migraine, Tension headache

Herpes simplex contains: Oral herpes, Herpes virus infection, Herpes simplex

Hypertension contains: Hypertensive crisis, Hypertension, Blood pressure increased

Injection site reaction contains: Injection site bruising, Injection site reaction, Pruritus, Infusion site pain, Injection site discomfort, Injection site erythema, Infusion site erythema, Injection site rash, Application site erythema, Infusion site reaction, Infusion site bruising, Infusion site rash, Infusion site hemorrhage, Injection site discoloration, Injection site pain, Injection site pruritus, Injection site inflammation, Infusion site pruritus

Lymphocyte count decreased contains: Lymphocyte count decreased, Lymphopenia

Musculoskeletal pain contains: Neck pain, Musculoskeletal pain, Pain in extremity, Back pain, Pain, Spinal pain, Noncardiac chest pain, Musculoskeletal chest pain

Myalgia contains: Myalgia, Muscle spasms

Myasthenia gravis contains: Myasthenia gravis, Myasthenia gravis crisis

Nausea contains: Nausea

Pyrexia contains: Pyrexia, Hyperthermia, Body temperature increased

Rash contains: Rash, Rash papular, Rash erythematous

Upper respiratory tract infection contains: Nasopharyngitis, Rhinitis, Upper respiratory tract inflammation, Rhinorrhoea, Sinusitis, Upper respiratory tract infection

Urinary tract infection contains: Urinary tract infection, Cystitis, Urosepsis

Vomiting contains: Vomiting

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab; SOC, system organ class

Table 103. Subjects With Adverse Events by System Organ Class, Safety Population, Safety Pool S1, Studies MG0003, MG0004, MG0007

System Organ Class	RLZ Total N=196 n (%)
Nervous system disorders	120 (61.2)
Infections and infestations	94 (48.0)
Gastrointestinal disorders	89 (45.4)
General disorders and administration site conditions	87 (44.4)
Musculoskeletal and connective tissue disorders	64 (32.7)
Investigations	52 (26.5)
Skin and subcutaneous tissue disorders	37 (18.9)
Respiratory, thoracic and mediastinal disorders	34 (17.3)
Injury, poisoning and procedural complications	29 (14.8)
Vascular disorders	28 (14.3)
Metabolism and nutrition disorders	23 (11.7)
Eye disorders	16 (8.2)
Renal and urinary disorders	16 (8.2)
Blood and lymphatic system disorders	13 (6.6)
Ear and labyrinth disorders	10 (5.1)
Cardiac disorders	8 (4.1)
Immune system disorders	8 (4.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (4.1)
Reproductive system and breast disorders	7 (3.6)
Hepatobiliary disorders	6 (3.1)
Psychiatric disorders	5 (2.6)
Endocrine disorders	2 (1.0)
Product issues	1 (0.5)
Social circumstances	1 (0.5)
Surgical and medical procedures	1 (0.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined in the three studies as: MG0003 - as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of rozanolixizumab or after 8 weeks following the final dose of rozanolixizumab were not considered TEAEs, MG0004 - as any event that was not present before the first administration of rozanolixizumab or any unresolved event already present before the first administration of rozanolixizumab that worsened in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last rozanolixizumab administration in study subjects who discontinued the study or rozanolixizumab, MG0007 - defined as any AE starting on or after the time of first rozanolixizumab administration up to and including 8 weeks (56 days) after the last dose of each treatment cycle.

Duration: MG0003 to 6 weeks of treatment followed by 8 weeks observation period to total 14 weeks, MG0004 - first 6 weeks of all study subjects, MG0007 - is treatment period per cycle is 6 weeks followed by an observation period of up to 16 weeks totaling up to 22 weeks per cycle and repeat cycles as needed. The maximum number of cycles is 10 by data cutoff date.

For specific preferred terms, see the table "Patients With Adverse Events by System Organ Class and Preferred Term..."

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; RLZ, rozanolixizumab

17.7. 120-Day Safety Update (Cutoff Date October 7, 2022)

On February 3, 2023, the Applicant submitted 3 months of additional safety data from the OLE Study MG0007 between the original BLA submission data cutoff date July 8, 2022, and 120-day safety update data cutoff date October 7, 2022.

No new subjects were included in this safety update. There were no new treatment-emergent deaths in this safety update. Three additional subjects discontinued treatment due to TEAEs of appendicitis and endocarditis in one subject each in rozanolixizumab ≈ 10 mg/kg group and intestinal adenocarcinoma in one subject in rozanolixizumab ≈ 7 mg/kg group. The description of endocarditis leading to death was included in the original BLA submission (Section [17.3](#)). No new cases of aseptic meningitis were identified. Four additional subjects developed serious TEAEs since the original BLA submission including intestinal adenocarcinoma (n=1) and nephrolithiasis (n=1) in rozanolixizumab 7 mg/kg group, and MG (n=1) and appendicitis (n=1) in rozanolixizumab 10 mg/kg group.

Compared to original BLA submission, there were no clinically significant changes in the relative incidence of common TEAEs ($\geq 5\%$ frequency) in the safety update. Most common TEAEs continued to be in the system organ class of nervous system disorders (headache, MG worsening), infections (upper respiratory tract infections, oral herpes, COVID-19), gastrointestinal disorders (diarrhea, nausea, abdominal pain, vomiting), and general disorders and administration site conditions.

There were two new TEAEs of decreased blood immunoglobulin which is expected given the mechanism of drug action; one event led to temporary drug discontinuation. The hematology parameters showed a decrease in the mean platelet counts during treatment period which returned to baseline by day 99. The mean change from baseline to day 43 in the platelet counts ($10^9/L$) was -11.2 in rozanolixizumab 7 mg/kg group (n=80) and -24.7 in rozanolixizumab 10 mg/kg group (n=77) which is comparable to the data in the original BLA submission. The reviewer notes that the maximum lowest mean platelet count was $248.6 \times 10^9/L$ on day 43 in the subjects treated with rozanolixizumab for either dose, which was still within the normal reference range 150 to $400 \times 10^9/L$, therefore reduction in the platelet counts were not clinically significant in the subjects receiving repeat treatment cycles of rozanolixizumab.

The mean lipid levels remained stable over time. The reductions in serum albumin levels remained less than 5% of baseline values and were not considered clinically meaningful.

No clinically significant changes were identified in vital signs and 12-lead electrocardiograms.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

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

As further described in the clinical inspection summary report from the Office of Scientific Investigations, the clinical sites of Drs. Bril, Druzdz, and Pascuzzi, and the Applicant, UCB Inc., were inspected in support of this BLA and covered protocol MG0003. The study appears to have been conducted adequately, and the data generated by these sites and submitted by the Applicant appear acceptable in support of the respective indication. The procedures used to maintain the blind even when blinded staff primed the infusion line appear adequate.

Primary efficacy data, Myasthenia Gravis-Activities of Daily Living (MG-ADL), and secondary efficacy data, Quantitative Myasthenia Gravis (QMG), were verified; no discrepancies were identified between source and Applicant's data for the double-blind treatment phase of the study. Discrepancies in efficacy data were identified during observation period due to incorrect scores entered into the eCRF at Dr. Bril's site. One subject had an increase in prednisone dose during observation period which was considered a protocol deviation at Dr. Pascuzzi's site. According to the Applicant, there was one incident of accidental unblinding caused by an employee during observation period. However, these discrepancies should not impact the overall efficacy analysis because these events occurred after the subjects had completed the double-blind treatment period which was the timepoint of interest for the primary and secondary efficacy endpoints in Study MG0003. Additionally, there was no evidence of under-reporting of adverse events.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 104](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 104. Key Labeling Changes and Considerations

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant's Draft PI
BOXED WARNING	• Not applicable.
1 INDICATIONS AND USAGE	• No substantial changes.

2 DOSAGE AND ADMINISTRATION

- A “Recommended Vaccination” subsection (2.1) was added based on the recommendation in the Guidance for Industry, Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, that if there is important information about administering other drugs before initiating the subject drug, that information should be included in this section.
 - In the recommended dosage table (Table 1), the following revisions were made:
 - (b) (4) was removed given the typical body weight of adults, for which the drug will be indicated.
 - A column for “Volume to be Infused” was added to complete the dosing information to help mitigate medication errors.
 - A new weight category of “100 kg and above” with a recommended dosage of 840 mg was added. For patients in this weight category, the efficacy of rozanolixizumab at the proposed fixed dose regimen of (b) (4) mg cannot be reliably predicted; therefore, the recommended dosage for patients weighing over 100 kg was revised to 840 mg, as evaluated in Study MG0003.
 - To provide additional guidance on the administration of subsequent cycle, the following statement was added: “The safety of initiating subsequent cycles sooner than 63 days from the start of the previous treatment cycle has not been established.”
 - The Applicant had proposed a subsection titled “(b) (4)”. The information proposed under this subsection was moved to the appropriate respective locations in the Dosage and Administration section.
 - Under the “Preparation and Administration Instructions” subsection (2.3), the following revisions were made:
 - Information was reordered to better align with the steps to be taken for preparation and administration of the drug.
 - Figures and text that is standard medical practice for healthcare providers was removed.
 - The time recommended to allow the vials to reach room temperature was revised from “(b) (4)” to “approximately 30 minutes” because it was confirmed that 30 minutes is enough time for the vials to reach room temperature.
 - Text was added to inform healthcare providers that the dose should be administered within 4 hours of puncturing the vial (removing the contents) or be discarded. Lack of microbial data does not support a longer time period. In addition, text was added to inform healthcare providers to administer the drug immediately after priming.
-

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
4 CONTRAINDICATIONS	○ Text regarding monitoring for hypersensitivity reactions was added; see comment under the Warnings and Precautions section. • No changes. • Infections (5.1): ○ The proposed statement that “(b) (4)” was removed; see the additions under Adverse Reactions. ○ Some data information regarding infections was relocated to section 6. ○ An “Immunization” heading was added; see comment under Drug Interactions. • Aseptic Meningitis (5.2): This adverse reaction was proposed by the Applicant for inclusion (b) (4)
5 WARNINGS AND PRECAUTIONS	(b) (4), the Division determined that there were two additional cases with rozanolixizumab in a different clinical program. Because the aseptic meningitis with rozanolixizumab led to hospitalization and discontinuation, a subsection was added to the Warnings and Precautions section for this serious adverse reaction. • Hypersensitivity Reactions (5.3): This subsection was added by the Division because clinically significant hypersensitivity reactions, including angioedema and rash, occurred with Rystiggo. Therefore, patients are to be monitored during administration and for a time period afterwards.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	- For safety exposure, in addition to the number of patients who received at least one dose of Rystiggo, the number of patients exposed to at least 5 and 10 treatment cycles was added. - In the common adverse reaction table, the Applicant had proposed (b) (4) (b) (4) (b) (4) (b) (4), the Division pooled the Rystiggo safety information and included only one column for adverse reactions that occurred with Rystiggo. - Adverse reactions for inclusion in the table were revised per pooling the Rystiggo data and the Division's safety assessment that included combining like terms for an accurate presentation of the adverse reactions. - Headings under the common adverse reaction table (i.e., (b) (4), Hypersensitivity Reactions, and Headache) were revised or added to include pertinent information regarding these safety issues. (b) (4) information was relocated; see comments under the Clinical Pharmacology section.
7 DRUG INTERACTIONS	The Applicant proposed (b) (4) (b) (4) (b) (4), this information was relocated to a heading in the Warnings and Precautions/Infections subsection (5.1).

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Pregnancy (8.1): The Applicant proposed (b) (4). The labeling was revised to state that there were embryonic death, reduced body weight, and impaired immune function in the pregnant monkeys administered doses of rozanolixizumab-noli at doses greater than those used clinically.
	Lactation (8.2): A statement was added that maternal IgG is known to be present in human milk.
	Pediatric Use (8.4): The Applicant proposed to include the phrase "(b) (4)". This phrase was deleted to align with the statement in CFR 201.57(c)(9)(iv)(F) and because, for prescription drug labeling, CDER defines the pediatric population as ages birth to 16 years (i.e., younger than 17 years old), as noted in the Guidance for Industry, Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling.
	Geriatric Use (8.5): The Applicant proposed to include a statement (b) (4). Therefore, the statement was revised to align with CFR 201.57(c)(9)(v)(B)(1) and the recommendations in the Guidance for Industry, Geriatric Information in Human Prescription Drug and Biological Product Labeling.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Not applicable.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
12 CLINICAL PHARMACOLOGY	• Mechanism of Action (12.1): No substantial changes. • Pharmacodynamics (12.2): ○ As the labeling is not to be promotional in tone [see CFR 201.56(a)(2)] the terms (b) (4) were removed. ○ The Applicant proposed (b) (4). This was deemed not necessary and removed. • Pharmacokinetics (12.3): ○ Revisions were made to follow recommendations in the Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (e.g., describing a dosage outside of the recommended range in terms of the highest recommended dose and using recommended headings and subheadings). ○ Revisions were made under the “Drug Interactions with Other Drugs or Biological Products” to align with statements in the Drug Interactions section (7.1). • Immunogenicity (12.6): This subsection was created, and information relocated to 12.6 (b) (4), as recommended in the Guidance for Industry, Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format.
13 NONCLINICAL TOXICOLOGY	• The comparison of the dose tested in monkey to that of the maximum recommended human dose was added.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
14 CLINICAL STUDIES	- The following background information regarding Study 1 was added: - Inclusion criteria regarding gMG therapy prior to screening and regarding minimum serum IgG levels - Baseline race demographics - The primary efficacy endpoint (Myasthenia Gravis-Activities of Daily Living [MG-ADL]) and the secondary (Quantitative Myasthenia Gravis [QMG]), both assessed as a change from baseline to day 43, were revised from being presented in (b) (4) efficacy table. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
17 PATIENT COUNSELING INFORMATION	Edits were made to align with the revisions and additions in the Warnings and Precautions section.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	- The suffix originally proposed, "(b) (4)", was revised to "-noli", which was found to be an acceptable suffix. - Text was revised to be clear and concise. - In the Description section (11): - The molecular weight was added. - In the How Supplied/Storage and Handling section (16): - A "Do not shake" statement was added because no data was submitted to support shaking of the drug product. - The phrase "to protect from light" was added to elaborate on why the product is to be stored in the original carton.

Source: Applicant's proposed PI received October 24, 2022

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

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

- Prescribing Information
- Carton
- Container

24. Postmarketing Requirements and Commitments

24.1. Postmarketing Requirements

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

PMR 4427-1

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to rozanolixizumab 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: 3/2024
- Final Protocol Submission: 1/2025
- Annual Interim Report Submissions: 1/2026
1/2027
1/2028
1/2029
1/2030
1/2031
1/2032
1/2033
1/2034
- Study Completion: 1/2035
- Final Report Submission: 1/2036

PMR 4427-2

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

PMR Milestones

- Draft Protocol Submission: 2/2024
- Final Protocol Submission: 9/2024

- Study Completion: 2/2026
- Final Report Submission: 7/2026

24.2. Postmarketing Commitments

The following postmarketing commitments were agreed upon by the Applicant:

PMC 4427-3

Develop a two-tiered reference standard system consisting of primary and working reference standards to support the rozanolixizumab product lifecycle. The primary and working reference standard will be created from representative DS batches which have passed all release specifications. The first new reference standards will be qualified against the current reference standard (b) (4) according to a predefined protocol. The results for qualification of new primary and working/secondary reference standards will be submitted in a Prior Approval Supplement. Alternatively, protocols for qualification and requalification of future primary and working/secondary reference standards may be submitted as a Prior Approval Supplement, which may facilitate a reduced reporting category for implementation of new reference standards.

PMC Milestones

- Final Report Submission: 2/2024

PMC 4427-4

Perform a shipping validation study under real time shipping conditions (i.e., temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using rozanolixizumab finished product in the final commercial container closure and packaging systems to verify the impact of shipping on the product quality of rozanolixizumab finished product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

PMC Milestones

- Final Report Shipping Conditions (Winter): 4/2024
- Final Report Shipping Conditions (Summer): 7/2024

25. Financial Disclosure

Table 105. Covered Clinical Studies: Study MG0003

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): 0		
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: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
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)

26. References

26.1. Literature

Barohn, RJ, D McIntire, L Herbelin, GI Wolfe, S Nations, and WW Bryan, 1998, Reliability testing of the quantitative myasthenia gravis score, Ann N Y Acad Sci, 841:769-772, <https://www.ncbi.nlm.nih.gov/pubmed/9668327>.

Burns, TM, M Conaway, DB Sanders, MG Composite, and M-QS Group, 2010, The MG Composite: A valid and reliable outcome measure for myasthenia gravis, Neurology, 74(18):1434-1440, <https://www.ncbi.nlm.nih.gov/pubmed/20439845>.

Furst, DE, 2009, Serum immunoglobulins and risk of infection: how low can you go?, Semin Arthritis Rheum, 39(1):18-29, .

Gilhus, NE, S Tzartos, A Evoli, J Palace, TM Burns, and J Verschuuren, 2019, Myasthenia gravis, Nat Rev Dis Primers, 5(1):30, <https://www.ncbi.nlm.nih.gov/pubmed/31048702>.

Isabwe, GAC, M Garcia Neuer, L de Las Vecillas Sanchez, DM Lynch, K Marquis, and M Castells, 2018, Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes, J Allergy Clin Immunol, 142(1):159-170 e152, <https://www.ncbi.nlm.nih.gov/pubmed/29518427>.

Kassardjian, CD, J Widdifield, JM Paterson, A Kopp, C Nagamuthu, C Barnett, K Tu, and A Breiner, 2020, Serious infections in patients with myasthenia gravis: population-based cohort study, *Eur J Neurol*, 27(4):702-708, <https://www.ncbi.nlm.nih.gov/pubmed/31997519>.

Men, CJ, AL Kossler, and ST Wester, 2021, Updates on the understanding and management of thyroid eye disease, *Ther Adv Ophthalmol*, 13:25158414211027760, <https://www.ncbi.nlm.nih.gov/pubmed/34263138>.

Muppidi, S, NJ Silvestri, R Tan, K Riggs, T Leighton, and GA Phillips, 2022, Utilization of MG-ADL in myasthenia gravis clinical research and care, *Muscle Nerve*, 65(6):630-639, <https://www.ncbi.nlm.nih.gov/pubmed/34989427>.

Pintea, I, C Petricau, D Dumitrascu, A Muntean, DC Branisteanu, DE Branisteanu, and D Deleanu, 2021, Hypersensitivity reactions to monoclonal antibodies: Classification and treatment approach (Review), *Exp Ther Med*, 22(3):949, <https://www.ncbi.nlm.nih.gov/pubmed/34335891>.

Prior, DE, E Nurre, SL Roller, D Kline, R Panara, AM Stino, JA Davis, ML Freimer, and WD Arnold, 2018, Infections and the relationship to treatment in neuromuscular autoimmunity, *Muscle Nerve*, 57(6):927-931, <https://www.ncbi.nlm.nih.gov/pubmed/29211921>.

Salari, N, B Fatahi, Y Bartina, M Kazeminia, R Fatahian, P Mohammadi, S Shohaimi, and M Mohammadi, 2021, Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis, *J Transl Med*, 19(1):516, <https://www.ncbi.nlm.nih.gov/pubmed/34930325>.

Sipila, JOT, M Soilu-Hanninen, P Rautava, and V Kyto, 2019, Hospital admission and prevalence trends of adult myasthenia gravis in Finland in 2004-2014: A retrospective national registry study, *J Neurol Sci*, 407:116520, <https://www.ncbi.nlm.nih.gov/pubmed/31639531>.

26.2. Other

MGFA, 2015 Professionals: Clinical Overview of MG, Myasthenia Gravis Foundation Of America (MGFA), accessed, 2023, <https://myasthenia.org/Professionals/Clinical-Overview-of-MG>.

26.3. Prescribing Information

Argenx, 2021 Prescribing Information: VYVGART, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761195s000lbl.pdf.

27. Review Team

Table 106. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Annie Nguyen/IA; Roshell Weatherless-Stroble/IA; Heather Bullock/IA (CPMS)
Nonclinical reviewer	LuAnn McKinney/IA
Nonclinical team leader	Lois Freed/IA
OCP reviewer(s)	Adarsh Gandhi/IA, Jie Liu/IA
OCP team leader(s)	Gopichand Gottipatti/IA; Bilal AbuAsal/IA,; Atul Bhattaram/IA
Clinical reviewer	Ami Mankodi/IA
Clinical team leader	Laura Jawidzik/IA
Biometrics reviewer	Ye Li/IA
Biometrics team leader	Kun JinJohn Lawrence/IA
Cross-disciplinary team leader	Laura Jawidzik/IA
Division director (pharm/tox)	Lois Freed/IA
Division director (OCP)	Mehul Mehta/IA
Division director (OB)	Jim Hung/IA
Division director (clinical)	Emily Freilich/IA
Office director (or designated signatory authority)	Teresa Buracchio/IA

Abbreviations: CPMS, Chief, Project Management Staff; IA, Integrated Assessment; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 107. Additional Reviewers of Application

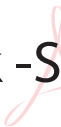
Office or Discipline	Name(s)
OPQ	Sheena Wang (ATL)
Microbiology Drug Substance	Joao Pedras Vasconcelos; Sheena Wang (TL)
Drug Product	Thomas Biel; Ash Rao (TL)
OBP Labeling	Scott Dallas
OPMA (Microbiology/Facility Reviewer)	Hamet Toure; Madushini Dharmasena (Micro TL); Michael Shanks (Facility TL)
OPDP	Annette Egbonim; Aline Moukhtara (TL)
OSI	Cara Alfaro; Phillip Kronstein (TL)
OSE/DEPI	Catharine Callahan; Kira Leishear (TL)
OSE/DMEPA	Chad Morris; Stephanie Degraw (TL)
OSE/DRISK	Donella Fitzgerald; Jacqueline Sheppard (TL)
Other	DDS: Sally Jo Yasuda; Medical Editor: Noah Whiteman, Joseph Dorn; Nikki Nichols Clinical Data Scientist: Christopher Jay, Alena (Qunshu) Zhang; Tracy Peters: Associate Director of Labeling/IA

Abbreviations: ATL, application team lead; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; 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 Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; TL, team lead

27.1. Reviewer Signatures

See next page.

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Signatory Authority	Teresa Buracchio OND ON	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Emily R. Freilich -S Digitally signed by Emily R. Freilich -S Date: 2023.06.21 14:31:28 -04'00' On behalf of Teresa Buracchio					
Clinical Division Director (Acting)	Emily Freilich ON DNI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Emily R. Freilich -S Digitally signed by Emily R. Freilich -S Date: 2023.06.21 14:31:57 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Cross-Disciplinary Team Lead	Laura Jawidzik OND DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Digitally signed by Laura A. Jawidzik -S Date: 2023.06.22 12:39:22 -04'00'					
Clinical Reviewer	Ami Mankodi OND DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 2, 3, 4, 6, 7, 8, 15,17, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Digitally signed by Ami K. Mankodi -S Date: 2023.06.22 12:52:27 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Primary Reviewer	Adarsh Gandhi OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Gopichand Gottipati -S On Behalf of Adarsh Gandhi Digitally signed by Gopichand Gottipati -S Date: 2023.06.20 20:15:47 -04'00'					
Clinical Pharmacology Team Leader	Bilal AbuAsal OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Bilal Abu Asal -S Digitally signed by Bilal Abu Asal -S Date: 2023.06.20 13:21:19 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Gopichand Gottipati OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Gopichand Gottipati -S  Digitally signed by Gopichand Gottipati -S Date: 2023.06.20 13:25:34 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology/Pharmacometrics Primary Reviewer	Jie Liu OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Jie Liu -S Digitally signed by Jie Liu -S Date: 2023.06.20 13:49:17 -04'00'					
Clinical Pharmacology/Pharmacometrics Team Leader	Atul Bhattaram OCP DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Venkatesh A. Bhattaram -S Digitally signed by Venkatesh A. Bhattaram -S Date: 2023.06.20 14:24:30 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Primary Reviewer	Mohsen Rajabiabhari OTS OCP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Mohsen Rajabi-abhari -S Digitally signed by Mohsen Rajabi-abhari -S Date: 2023.06.20 14:07:38 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/Toxicology Team Leader	David Carbone ON DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13.1 and 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: David L. Carbone -S Digitally signed by David L. Carbone -S Date: 2023.06.23 19:05:14 -04'00'					
Pharmacology/Toxicology Reviewer	LuAnn McKinney ON DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13.1 and 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Luann Mckinney -S Digitally signed by Luann Mckinney -S Date: 2023.06.23 18:43:24 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/Toxicology Division Director	Lois Freed ON DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13.1 and 13.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Lois M. Freed -S Digitally signed by Lois M. Freed -S Date: 2023.06.23 19:32:15 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Team Leader	John Lawrence OB DBI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: John P. Lawrence -S Digitally signed by John P. Lawrence -S Date: 2023.06.21 10:15:52 -04'00'					
Biometrics Reviewer	Ye Li OB DBI	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: Section 5 Efficacy (Evaluation of Benefit) Section 15.1 Subgroup Analyses for the Primary Efficacy Endpoint, Study MG0003	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Ye Li -S (Affiliate) Digitally signed by Ye Li -S (Affiliate) Date: 2023.06.20 14:56:51 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Associate Director for Labeling	Tracy Peters ON DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Digitally signed by Tracy Peters -S Date: 2023.06.22 21:48:14 -04'00'					
Product Quality Team Leader	Hailin (Sheena) Wang OBP DBRRIII	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:  Digitally signed by Hailin Wang -S Date: 2023.06.21 20:50:48 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Other Deputy Director of Safety	Sally Jo Yasuda ON DNI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: PMRs	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sally U. Yasuda -S  Digitally signed by Sally U. Yasuda - Date: 2023.06.20 13:56:00 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Regulatory Project Management CPMS	Heather Bullock ON DNI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Heather M. Bullock -S Digitally signed by Heather M. Bullock -S Date: 2023.06.23 16:25:11 -04'00'					
Regulatory Project Management Regulatory Project Manager	Annie Nguyen ON DNI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Roshell J. Weatherless-stroble -S Digitally signed by Roshell J. Weatherless-stroble -S Date: 2023.06.21 14:45:13 -04'00' On behalf of Annie Nguyen					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Regulatory Project Management Regulatory Project Manager	Roshell Weatherless-Stroble ON DNI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Roshell J. Weatherless-stroble -S  Digitally signed by Roshell J. Weatherless-stroble -S Date: 2023.06.21 14:45:34 -04'00'					

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

/s/

LAURA A JAWIDZIK
06/26/2023 06:35:10 PM