09 November 2023
EMA/CHMP/535512/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rystiggo

International non-proprietary name: Rozanolixizumab

Procedure No. EMEA/H/C/005824/0000

Note

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

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List of abbreviations

AChE	Acetylcholinesterase
AChR	Anti-acetylcholine receptor
ADA	Antidrug antibodies
ADR	Adverse drug reactions
AESI	Adverse events of especial interest
(TE) (S)AEs	(Treatment-emergent) (serious) adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}72h}$	Area under the plasma concentration versus time curve from time 0 to 72 hours
AUC_{inf}	Area under the plasma concentration versus time curve from time 0 to infinite
$AUC_{tau,ss}$	Area under the concentration-time curve during a dosing interval at steady state
(S)(D)BP	(Systolic) (diastolic) blood pressure
C5	Complement 5
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration observed
$C_{max,ss}$	Maximum concentration during a dosing interval at steady state
CRO	Contract research organisation
C_{trough}	Trough concentration
CV	Cardiovascular
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eGRF	Estimated glomerular filtration rate
EMA	European Medicines Agency
E_{max}	Maximum effect
$E_{max,MGADL}$	Maximum effect on MG-ADL at a complete reduction of total IgG
ePPND	Enhanced pre- and post-natal development study
EOS	End of study
EQ-5D-5	5-level Euro Quality of Life 5 Dimension
ES	Enrolled set
FAS	Full analysis set
Fab’	Fragment antigen binding
FcRn	Neonatal fragment crystallisable receptor
FIH	First-in human
GI	Gastrointestinal
GLP	Good laboratory practice
gMG	generalised myasthenia gravis
GOF	Goodness-of-fit
HED	Human equivalent dose
hFcRn Tg	human FcRn-transgenic
hIgG	human IgG
HCV	Hepatitis C virus
HDL	High-density lipoprotein
ICH	International Council for Harmonisation
IC_{50}	50% inhibitory concentration
IDMC	Independent Data Monitoring Committee
IIV	Inter-individual variability

IgG	Immunoglobulin G
IMP	Investigational medicinal product
ITP	Immune thrombocytopenia
IV	Intravenous(ly)
IVIg	Intravenous immunoglobulin
KLH	Keyhole limpet haemocyanin
LC-MS/MS	Liquid chromatography – tandem mass spectrometry/mass spectrometry
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
LS	Least square
mAb	Monoclonal antibody
MAT	Mean absorption time
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	Myasthenia gravis activities of daily living
MGC	Myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	15-item quality of life scale for myasthenia gravis
MGII	Myasthenia Gravis Impairment Index
MMRM	Mixed model for repeated measures
MoA	Mechanism of action
MOG-AD	Oligodendrocyte glycoprotein-associated disease
MuSK	Muscle-specific tyrosine kinase
Nab	Neutralising antibodies
NCA	Non-compartmental analysis
NHP	Nonhuman primates
NMJ	Neuromuscular junction
OECD	Organization for Economic Cooperation and Development
OLE	Open label extension
PK-PPS	Pharmacokinetic per-protocol set
PT	Preferred term
QMG	Quantitative myasthenia gravis
QoL	Quality of life
QTc(F)	(Fridericia) corrected QT interval
RS	Randomised set
SC	Subcutaneous(ly)
SCLE	Subcutaneous lupus erythematosus
SOC	System organ class
SS	Safety set
pcVPC	Prediction corrected visual predictive check
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PLEX	Plasma exchange
PND	Postnatal day
PopPK(PD)	Population PK(PD)
PRO	Patient-reported outcomes
RNA	Ribonucleic acid
RUV	Residual unexplained variability

SmPC	Summary of product characteristics
TBL	Total bilirubin
TCR	Tissue cross reactivity
TDAR	T-dependent antibody response
TK	Toxicokinetic
TMDD	Target mediated drug disposition
UCB7665	Rozanolixizumab
ULN	Upper limit of normal
UTI	Urinary tract infection
V/F	Apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma submitted on 3 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Rystiggo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 December 2020.

Rystiggo was designated as an orphan medicinal product EU/3/20/2272 on 22 April 2020 in the following condition: treatment of myasthenia gravis.

The applicant applied for the following indication:

Rystiggo is indicated for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive and require therapy in addition to corticosteroids or non-steroidal immunosuppressants.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0410/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0410/2022 was not yet complete as some measures had been deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance rozanolixizumab contained in the above medicinal product

to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 May 2019	EMEA/H/SA/4099/1/2019/III	Elena Wolff-Holz André Elferink
16 December 2021	EMA/SA/0000060999	Rosalía Ruano Camps Ole Weis Bjerrum Armando Magrelli

The applicant received scientific advice on the development of rozanolixizumab for the treatment of myasthenia gravis from the CHMP on 29 May 2019 (EMEA/H/SA/4099/1/2019/III). The scientific advice pertained to the following clinical, non-quality aspects:

- Agreement that UCB has conducted a comprehensive nonclinical programme of pharmacological, PK/PD, and toxicity studies for Rozimab, including a GLP-compliant tissue cross-reactivity study (with human and Cynomolgus monkey tissues), and GLP-compliant 4-, 13-, and 26-week toxicology studies (the latter in sexually mature animals) in Cynomolgus monkeys. UCB has also initiated an ePPND study in the Cynomolgus monkey, including assessment for the potential for immunotoxicity in the offspring with immunophenotyping and a T cell dependent antibody (IgG) response (TDAR) test.
- Agreement that UCB considers that MG0002 established supportive evidence of efficacy with Rozimab for the treatment of gMG. UCB intends to confirm the efficacy of Rozimab in patients with MG with another randomised, placebo-controlled study (MG0003), which will be followed by an OLE study, MG0004.

The applicant received scientific advice on the development of rozanolixizumab for the treatment of myasthenia gravis from the CHMP on 16 December 2021 (EMA/SA/0000060999). The scientific advice pertained to the following clinical, quality, significant benefit aspects:

- Quality: the proposed methodology to justify the non-similarity of rozanolixizumab and efgartigimod; the proposed methodology to justify the non-similarity of rozanolixizumab and eculizumab.
- Adequacy of the envisaged safety database to support an MAA for the treatment of gMG; rationale and adequacy of data obtained on home Healthcare Professional (HCP) rozanolixizumab administration from MG0007 (OLE study) to support administration by HCP upon physician's discretion.
- Demonstration of significant benefit of rozanolixizumab over standard of care medications, off-label use products, eculizumab, ravulizumab, plasma exchange, efgartigimod.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Robert Porszasz

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Maria del Pilar Rayon

The application was received by the EMA on	3 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 February 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	6 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	5 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rystiggo on	09 November 2023
The CHMP adopted a report on similarity of Rystiggo with Soliris and Vyvgart on (see Appendix on similarity)	09 November 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	09 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Generalised myasthenia gravis (gMG) is a rare, chronic, neuromuscular autoimmune disease.

2.1.2. Epidemiology and risk factors

Myasthenia gravis most commonly affects young adult women (aged under 40 years) and older men (aged over 60 years), but it can occur at any age. Epidemiological studies reveal an increasing prevalence over the past 50 years, due in part to an increase in the frequency of diagnosis in the elderly (Sanders et al, 2016). As the population has aged, the average age at onset has increased correspondingly.

Information from Orphanet (last updated: 2022-07-28) suggests that the prevalence of MG in the EU is estimated to be 1 per 5,000 population.

2.1.3. Aetiology and pathogenesis

Myasthenia gravis is an organ-specific, antibody-mediated autoimmune disease. The pathogenic autoantibodies against the AChR are primarily of the immunoglobulin G (IgG)1 or IgG3 isotype and induce a complement-dependent, T-cell mediated immunological attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (NMJ) resulting in a decrease in the number of available AChR. In addition, the postsynaptic folds are flattened, or "simplified."

Although acetylcholine is released normally, this leads to a decreased efficiency of neuromuscular transmission, ending in reduced endplate potentials which results in the clinical phenotype of skeletal muscle weakness and fatigability.

MuSK is an NMJ protein that is specifically expressed at the postsynaptic membrane, where it colocalises with AChR, and plays a critical role in the maintenance of the normal functional integrity of the NMJ by mediating clustering of AChR (Zong et al, 2012). The inhibition of MuSK synthesis has been found to cause AChR dispersion and endplate disruption (Lazaridis and Tzartos, 2020). The autoantibodies against MuSK are primarily IgG4s and do not induce complement activation; rather they are hypothesised to prevent the assembly of functional protein complexes at the NMJ, thereby inhibiting AChR clustering (Shiraishi et al, 2005).

While the precise mechanism of initiation and maintenance of auto-sensitisation to the AChR is not clear, abnormalities of the thymus gland (hyperplasia and neoplasia) almost certainly play a role in the majority of MG patients (Meriggioli and Sanders, 2012). As a primary site for the establishment of immune regulation, derangements in the thymus gland may lead to a defect in the immune system's suppression of autoreactive lymphocytes, allowing for the development of anti-AChR immune responses.

Approximately 80 to 85% of all MG patients are positive for anti-AChR antibodies and approximately 5 to 8% (Rodolico et al, 2020; Rodriguez et al, 2015; Meriggioli and Sanders, 2012) are positive for anti-MuSK antibodies.

Some patients do not have detectable antibodies against any of these antigens, being referred to as seronegative MG. Antibodies against various other extracellular or intracellular targets are found in

several MG patients (e.g, agrin, colQ, Kv1.4, titin). MG pathogenesis, its clinical presentation and the response of patients to therapy vary depending on the pattern of autoantibodies detected.

2.1.1. Clinical presentation, diagnosis

Myasthenia gravis is a long-term debilitating condition often associated with thymic follicular hyperplasia or thymoma.

In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 MG patients, symptoms remain limited to extrinsic ocular muscles (ocular myasthenia gravis). However, in more than 80% of patients, the symptoms progress within 2 years to affect other bulbar muscles as well as limb muscles (gMG).

The generalised muscle weakness leads to difficulties in mobility, speech, swallowing, and vision, as well as impaired respiratory function and extreme fatigue. Up to 20% of patients experience potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation.

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

2.1.2. Management

First-line treatment for MG is symptomatic with acetylcholinesterase (AChE) inhibitors such as pyridostigmine bromide. This and other AChE inhibitors directly increase the concentration of acetylcholine at the NMJ and thereby improve signal transmission through increased engagement of postsynaptic acetylcholine receptors. While this mechanism of action (MoA) can provide direct and rapid symptomatic relief, most patients develop dose-limiting cholinergic side-effects due to overstimulation of the autonomic nervous system. The short-acting nature of pyridostigmine requires multiple daily dose administrations which can become burdensome for patients.

Immunosuppressive treatment of gMG is dominated by untargeted treatments such as steroids and nonsteroidal immunosuppressants (e.g, azathioprine). Both steroids and nonsteroidal immunosuppressants target the immune system non-specifically with the goal of reducing autoimmune reactivity in MG. Treatment with these agents are associated with well-documented short-term as well as long-term toxicities (Gilhus et al, 2019). The delayed beneficial effect combined with early onset of tolerability issues frequently discourages patients from continuing therapy.

Both plasma exchange (PLEX) and intravenous immunoglobulin (IVIg) are considered for patients with gMG who have exhausted all their other treatment options, and whose clinical status is deteriorating despite ongoing immunosuppressive and AChE inhibitor therapies. The availability of IVIg (ie, shortages; increasing demand over supply) and repetitive cycles of IVIg and PLEX administered in a hospital setting are burdensome, and time consuming for patients, caregivers and healthcare professionals and are not considered a viable long-term treatment option for most patients with MG (Gilhus and Verschuuren, 2015).

Rituximab, an anti-CD20 monoclonal antibody (mAb) is reserved for patients that are refractory to conventional oral immunosuppressants and used as part of an escalation therapy, which is supported in

the International Consensus guidance (Narayanaswami et al, 2021). Safety concerns related to the risk of virus-related progressive multifocal leukoencephalopathy remain.

Biologics have added to the more targeted treatment options for gMG, with eculizumab (Soliris) being a first-in-class humanised mAb targeting the terminal complement complex, blocking the enzymatic cleaving of complement 5 (C5) and thereby preventing the activation of the complement complex. During this procedure, Zilbrysq (zilucoplan) has also been authorised for the treatment of gMG in adult patients who are AChR antibody positive. Due to lack of complement involvement in the pathophysiology of anti-MuSK+ patients with gMG, this difficult-to-treat subgroup of patients does not benefit from C5 inhibitor treatment.

The most recent additions to the MG treatment regimen have been the introduction of efgartigimod (Vyvgart) being an IgG1 Fc fragment targeting neonatal fragment crystallizable receptor (FcRn) leading to reduced overall IgG recycling, and ravulizumab being a recombinant mAb that inhibits terminal complement activation at the C5 protein.

Patients with gMG are significantly affected by the burden of their unpredictable symptoms which negatively impacts their lives while receiving conventional treatment. In addition to the burden imposed by symptoms, patients with gMG may also experience a substantial treatment burden from currently available therapies across the entirety of the treatment pathway.

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

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

Thus, a significant unmet medical need still exists in gMG subpopulations for an effective treatment with rapid onset of action, good tolerability and acceptable safety profile and increased convenience.

2.2. About the product

Rozanolixizumab drug substance is a recombinant, humanised anti-neonatal Fc receptor (FcRn) IgG4P mAb. The nomenclature IgG4P signifies that the IgG4 heavy chain sequence has been modified in its hinge region by mutating serine at position 241 to proline in order to reduce the occurrence of fragment antigen binding (Fab') arm exchange (separation of the 2 heavy chain- light chain pairs of the IgG followed by reassociation with equivalent heavy-light chain pairs of IgG4 of different specificity).

The Fab' domain of rozanolixizumab has been crystallised in complex with human FcRn (extracellular domain) (Smith et al, 2018) to demonstrate (i) the structure of the Fab' is typical of Fab' structures in general, and (ii) its binding site on human FcRn α-chain overlaps with the site known to bind the Fc domain of IgG, indicating that rozanolixizumab inhibits IgG binding to FcRn by competition for the binding site. Rozanolixizumab does not bind to, or close to, the site on FcRn that binds albumin and consequently does not inhibit albumin recycling.

The natural ligands of FcRn are IgG and albumin which, following pinocytic uptake into the endosomes of a wide variety of cells including endothelial cells and haematopoietic cells, are salvaged by FcRn, which traffics these proteins away from the lysosome to be released back into the plasma instead of becoming degraded.

The applicant is developing rozanolixizumab for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive. The MoA of rozanolixizumab is whereby blockade of FcRn leads to enhanced catabolism of IgGs, with the aim to reduce pathogenic autoantibodies in autoimmune diseases. Data shows that rozanolixizumab markedly lowers serum IgG and IgG autoantibody levels in patients with gMG.

Pharmacological classification : Immunosuppressants, Monoclonal antibodies, ATC code: L04AG16

The initially claimed indication wording for rozanolixizumab is as follows:

The treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive and require therapy in addition to corticosteroids or non-steroidal immunosuppressants.

The finally approved indication wording for rozanolixizumab is as follows:

As an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

The following table indicates the recommended total weekly dose of Rystiggo according to the patient's body weight:

Body weight	≥ 35 to <50 kg	≥ 50 to < 70 kg	≥ 70 to < 100 kg	≥ 100 kg
Weekly dose (mg)	280 mg	420 mg	560 mg	840 mg
Weekly dose (ml)	2 ml	3 ml	4 ml	6 ml
Number of vials to be used*	1	2	2	3

*Each vial contains excess volume for priming of the infusion line, see "Method of administration".

2.3. Type of application and aspects on development

The applicant received scientific advice on the development of rozanolixizumab for the treatment of myasthenia gravis from the CHMP on 16/12/2021 (EMA/SA/0000060999) and on 29/05/2019 (EMEA/H/SA/4099/1/2019/III). See above.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a sterile, preservative-free, colourless to pale brownish yellow, clear to slightly opalescent solution for subcutaneous injection, containing 140 mg/mL rozanolixizumab as active substance. Other ingredients are histidine, histidine hydrochloride monohydrate, proline polysorbate 80 and water for injections.

The finished product is available as a single-use Type I glass vial with a stopper (rubber) sealed with a crimp seal and flip off cap, containing 2 mL of solution (280 mg rozanolixizumab). Pack size of 1 vial.

2.4.2. Active Substance

2.4.2.1. General Information

Rozanolixizumab (INN) is a humanised IgG4P mAb that binds with high affinity to the FcRn at both neutral and acidic pH, and thereby inhibits the activity of FcRn without blocking the binding and recycling of albumin. By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG autoantibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG autoantibodies.

Rozanolixizumab is produced in the CHO DG44 cell line and consists of two heavy chains and two light chains. The nomenclature IgG4P signifies that the IgG4 heavy chain sequence has been modified in its hinge region by mutating serine at position 225 to proline to prevent Fab arm exchange, improving hinge stability. IgG4 antibodies naturally have very low effector function, and *in vitro* experiments show no evidence of cytokine release induced by rozanolixizumab.

2.4.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The rozanolixizumab active substance is manufactured at Samsung BioLogics Co. Ltd, Incheon, Republic of Korea. Sufficient evidence of GMP compliance has been provided for all sites involved in the active substance manufacturing and/or control.

Rozanolixizumab is manufactured using an upstream process resembling a standard process for mAb manufacturing based on fed-batch culturing of recombinant CHO cell lines. The production bioreactor content is harvested by centrifugation and filtration to remove cells and cell debris, and 0.2µm filtered prior to further purification.

The purification steps are typical for mAb manufacturing with chromatography steps and orthogonal virus reduction steps. The process pool is then concentrated and filtered and finally mixed with excipient buffer. The protein concentration is adjusted with formulation buffer. The formulated active substance is finally 0.2µm filtered into bags and stored at ≤-60°C. Active substance is shipped to the finished product manufacturing facility in insulated boxes at ≤-60°C using qualified procedures.

Critical process parameters (CPPs) and process parameters (PPs) have been identified for the upstream process and for the purification process. Criticality of each process step has been evaluated and defined based on the critical quality attributes (CQA) and a justification for the classification is provided. The

identified PPs and CPPs, and their associated normal operating ranges and proven acceptable ranges, are considered acceptable.

The IPCs and associated acceptance criteria or action limits are found adequate. The analytical procedures used for IPCs, and their respective method validation, are summarised and the information provided is found sufficient.

Controls for all the critical steps have been established to ensure consistent quality of rozanolixizumab active substance produced by the commercial manufacturing process.

Raw materials and cell banks

Compendial and non-compendial raw materials are used in the manufacturing process. Compendial raw materials are tested according to quality standard (Ph. Eur., JP or USP). Specifications are provided for all non-compendial raw materials. The composition of the expansion medium and production medium is provided. All cell culture media prepared and feed preparations are tested for bioburden and endotoxin. The nature of filters and membranes as well as the material of the columns used in the manufacturing process are also provided.

Apart from the recombinant CHO production cells, no raw material of animal or human origin is used for the manufacture of rozanolixizumab active substance. It is informed that tallow derivatives used in the CryoTube screw caps and in the bags used for active substance storage have been manufactured with processing conditions that meet the criteria defined in EMA/410/01 (European Commission: *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*). The tallow-derived additives thus pose no risk for transmission of TSE. A TSE/BSE statement from the manufacturer of the CryoTubes is provided.

Rozanolixizumab is expressed from the cell clone, which was generated by stable transfection of the CHO DG44 host cell line with the expression plasmid encoding rozanolixizumab. The host cell line CHO DG44, which was adapted into a serum-free medium, was confirmed to be sterile and free from mycoplasma and adventitious viruses. These clones were then screened for the presence of human IgG. The screening and subcloning procedures have been described in sufficient details. After multiple rounds of evaluation, the cell clone was chosen to create the master cell bank (MCB). The generation of MCB and working cell bank (WCB) has been adequately described. Cells from the WCB are used to initiate the production process. A post-production cell bank (PPCB) was also generated to demonstrate the stability of the cell line.

The MCB, WCB and PPCB were characterised according to relevant guidelines, addressing microbial and viral purity, host cell identity and genetic stability. It is concluded that the generation and characterisation of MCB, WCB and PPCB comply with the requirements set in the ICH Q5A, Q5B and Q5D guidelines.

A procedure to establish and qualify future WCBs is provided and considered adequate.

Process validation

The validation of the rozanolixizumab active substance manufacturing process was performed. Four commercial process consecutive batches originating from four independent thaws of the WCB were manufactured in this process performance qualification (PPQ) campaign. The IPCs results, the unit operating ranges and the PPQ batch release data confirm that the manufacturing process performs as intended to consistently manufacture active substance meeting predefined quality attributes. All PPQ release data comply with the proposed active substance specification. Several deviations were observed. They were, however, sufficiently addressed, and it can be agreed that they did not have any impact on the overall qualification of the manufacturing process. Corrective actions have been implemented to mitigate risk of repeat occurrences of the process deviations.

Efficient clearance of process-related impurities was consistently demonstrated in all the four PPQ runs. In addition, analysis of product-related variants levels in in-process samples and in active substance was performed. The results provided show reliable control of product variants.

Acceptable ranges for in-process hold times were determined using physicochemical stability studies performed at small scale with three PPQ batches. For the physicochemical stability studies, the impact of the proposed hold times was evaluated on selected stability evolving parameters, as well as on pH and Conductivity, for the process steps at which the ranges of these parameters must be maintained following adjustment. Microbial hold times are said to be validated in the commercial-scale product pool vessels at Samsung using growth promoting surrogate media. However, the data provided on the media hold times studies as well as the additional risk analysis provided by the applicant were not found sufficient. The applicant committed to submit microbial data on bioburden and endotoxin levels by the end of Q3 2024 on commercial-scale active substance batches.

Sufficient information is provided on the reuse of chromatography resins and UF/DF membrane used in the active substance purification process. The number of reuse cycles was evaluated based on small-scale reuse studies and is concurrently verified at manufacturing scale, which is considered acceptable according to current guidance. Resin performance and ultrafiltration membrane performance were assessed. Overall, as the acceptance criteria for all the product quality attributes and yield were met, the proposed number of reuse cycles is accepted.

Blank cycles are performed at regular intervals to assess the efficiency of the cleaning procedures and potential carryover. No detectable carryover of product or of process-related impurities has been observed throughout small-scale and manufacturing-scale studies. It is therefore concluded that the established cleaning procedures are appropriate to avoid carryover between cycles of use.

A risk assessment to evaluate potential leachables/extractables originating from consumables used during the manufacture of active substance was performed and showed no safety risk. The shipping procedure of the active substance was qualified using a distribution simulation study, a thermal operational qualification study and a performance qualification study.

The analytical methods used in the process validation studies are sufficiently described.

In conclusion, the approach taken for validation of the upstream and downstream processes is in line with current guidelines. The PPQ data provided demonstrate that the commercial manufacturing process provides a product that consistently meets its predefined quality attributes, and that the process performs as designed. Process performance was demonstrated to be consistent and robust. The rozanolixizumab manufacturing process is therefore considered as validated at the commercial manufacturing site and scale provided the issue raised on the microbial hold times is solved.

Manufacturing process development

Developmental history

A number of different versions of the rozanolixizumab manufacturing process were developed. A comparability exercise including release testing, quantitative analytical characterisation, qualitative comparison of batches analysed side by side, and stress stability comparison, was performed to determine the impact of the manufacturing process changes on product quality in accordance to ICH Q5E. The quantitative analytical characterisation was conducted by various analytical methods to assess the primary, secondary and tertiary structure of rozanolixizumab, with predefined comparability acceptance criteria.

In addition, the same degradation profile was observed between processes in stressed conditions. Consequently, comparability between batches from different processes may be considered acceptable.

Overall, the comparability studies demonstrate comparability between the different active substance manufacturing processes.

The analytical method development for release and stability testing occurred in conjunction with the manufacturing process development. In preparation for the phase 3 clinical studies, the original analytical methods used to test the potency, identity, and purity parameters were redeveloped. Equivalence studies were performed to evaluate comparability of the original and redeveloped methods. The redeveloped methods provided an improved performance and were therefore applied for batch testing from the penultimate process onwards. This is supported.

For other analytical methods, it was evaluated that the changes were minor and therefore method equivalence studies were not required. This evaluation is considered acceptable.

Process characterisation studies

Process characterisation studies at laboratory scale have been performed for the active substance manufacturing process to increase process understanding, define the proven acceptable ranges (PARs) for process parameters and to identify CPPs that have a significant impact on the CQAs of the product.

A risk assessment was performed for each unit operation to define the process parameters that have a potential impact on the CQAs. These process parameters were further examined in process characterisation studies to define their PARs. Process characterisation studies were either univariate or multivariate studies planned and evaluated using design of experiment (DOE) concepts in qualified scale-down models. These studies were designed based on experience gained during the development of the active substance manufacturing process. For the parameters where a statistical impact on a CQA was demonstrated, an assessment of process significance was made by calculating the impact ratio.

The maximum allowable levels for each CQA applied in the assessment of the process characterisation studies are provided and justified. In addition, minimum allowable levels for step yields were defined for the relevant process steps and used to assess the process significance of the impact on yield and limit the PAR to increase process performance, if required.

Process characterisation studies were performed for the critical process steps.

Overall, the strategy applied for process characterisation, including the process parameters selected for investigation, the qualification strategy for the small-scale models (SSMs), and the conduction of the process characterisation studies, is considered comprehensive and appropriate. The CPPs identified in the process characterisation studies are considered adequate, and the SSMs representative of the large-scale process and suitable for performing the process characterisation studies.

Control strategy

The control strategy for the rozanolixizumab active substance manufacturing process was established in line with ICH Q11 guidance. A list of product quality attributes (PQAs) for rozanolixizumab was compiled based on the quality target profile, characterisation of the molecule, and knowledge gained during process development and manufacture. For each PQA, a risk assessment was performed to assess the impact on biological activity, Pharmacokinetics (PK) / Pharmacodynamics (PD), immunogenicity, and safety. A worst-case approach was taken, assuming that the PQA being assessed was present, i.e., the actual levels of a PQA or the capability of the process to reduce the levels of the PQA was not considered. A score was also assigned for the level of uncertainty of the impact assessment. The overall criticality rating of each PQA was the product of the impact and the uncertainty scores.

A risk-based approach was used to determine the level of control needed for each CQA to ensure appropriate product quality. The risk assessment encompassed levels observed during manufacturing and storage, and potential impact of the CQA on biological activity, PK/PD, immunogenicity, and safety.

The strategy used for identification and criticality assessment of the product quality attributes is considered thorough, and the identified CQAs are endorsed. The overall process control strategy involves controlling at all levels of the manufacturing process, i.e. control of facility and equipment, control of raw materials, media, buffers, resins, membranes, and filters, control of container closure system, specifications defined for release and stability testing, controls of unit operations and hold times which have been demonstrated to have an impact on product quality, in-process testing with corresponding acceptance criteria or action limits.

Overall, the manufacturing process is considered adequately described and the applied process parameters and in-process controls, as well as their ranges, and the control of starting materials are considered appropriate to control the process and ensure manufacture of active substance of consistent quality. Overall, the approach taken to validate rozanolixizumab manufacturing process is found adequate. The process is demonstrated to perform consistently and rozanolixizumab active substance meets all the biochemical, functional, and microbiological acceptance criteria. The process development, including development of the control strategy, is considered sufficiently described and justified. Comparability studies confirmed product comparability throughout development.

Characterisation

Elucidation of structure and other characteristics:

Structure, product variants, and biological activity were characterised. The batch mainly used for this is a PPQ batch, representing the commercial process, but with supportive batches also being used in initial studies on glycosylation, and for identification and characterisation of product variants.

Overall, the structure and other characteristics are well characterised.

Primary structure:

Intact mass analysis by LC-ESI-MS confirmed the expected masses. N-terminal sequencing by Edman degradation was carried out and showed the expected sequence. Tryptic peptide mapping by LC-ESI-MS was also carried out.

Glycosylation:

LC-ESI-MS tryptic peptide mapping and HILIC-UPLC carried out on enzymatically released glycans yielded comparable results concerning the types and abundance of glycoforms. Sialic acids released by acid hydrolysis were analysed by RP-UPLC.

Higher-order structure:

Disulphide bridges were analysed by tryptic peptide mapping by LC-ESI-MS on non-reduced samples. All were found to be configured as expected for a properly folded and assembled IgG4 molecule.

Secondary structure was studied by far UV CD and FTIR spectroscopy, tertiary structure by near UV CD and intrinsic fluorescence, and thermal stability by differential scanning calorimetry. The data suggest a globular protein with high β-sheet content, and unfolding characteristics typical of an IgG4 molecule.

Product-related species – size variants:

Size variants were studied by SE-HPLC, svAUC and NR-CGE. NR-CGE was used to further characterise LMWS. Biological activity of size variants: The SE-HPLC peaks were assessed for binding affinity by SPR and potency by cell-based assay.

Product-related species – charge variants:

The iCE profile of PPQ batch peaks affecting charge were characterised using tryptic peptide mapping by LC-ESI-MS. For identifying the contents of different product variants, in APG and BPG, in process samples

were purified and analysed for: Size variants by NR-CGE, sialic acid content by RP-UPLC, and tryptic peptide mapping by LC-ESI-MS.

Product-related species – oxidation:

Oxidation was studied using tryptic peptide mapping by LC-ESI-MS.

Biological activity:

The assay used to characterise potency is the same as used for release and stability testing of active substance and finished product. Rozanolixizumab was shown to have minimal Fc effector functions. This was confirmed by cytokine release studies. Based on literature data, considering that the binding of monomeric IgG4 to C1q is unlikely, no determination of the C1q binding was deemed necessary. This is endorsed.

Elucidation of structure– forced degradation studies:

The effects were tested of heat stress (up to 50°C), pH stress (pH 3, pH 10), deamidation, oxidation, agitation, light stress, and forced glycation on: Size variants, charge variants, higher-order structure and PTMs.

Impurities:

Product-related impurities:

HMWS (and also proteinaceous subvisible particles) were characterised as product-related impurities, while LMWS can be either product-related substances (species with intact Fab) or product-related impurities (species lacking intact Fab). HMWS and subvisible particles were included in the finished product release and shelf-life specification – HMWS also on active substance release specification. To monitor charge heterogeneity, charge variants were included on active substance and finished product release specification. Further information on classification and control strategies for product-related impurities is found in 3.2.S.2.6 – Manufacturing Process Development – Control Strategy.

Process-related impurities:

Process-related impurities include process leachables, cell-substrate derived impurities, process reagents/materials, and reagents from culture media and feeds (two proprietary media components). Residual levels of these impurities were measured during the PPQ campaign at select intermediate steps and final active substance (details in Section 3.2.S.2.5 –Process Validation and/or Evaluation – PPQ), except for the proprietary buffer components, where residual levels were instead estimated based on theoretical considerations. Small-scale clearance studies were furthermore performed during manufacturing process development (details in Section 3.2.S.2.6 Manufacturing Process Development – Small-scale Studies). For each impurity, the measured/estimated max dose per day were compared to the 'permitted daily exposure' (PDE) or 'no observed adverse event level' (NOAEL), and a safety factor was calculated. The safety factor was well above one for all impurities. The applicant committed to implement determination of the residual level of a process impurity as an IPC for all batches with the next manufacturing campaign. The quantification limit of the assay will be used. Until this IPC will be put in place, the applicant committed performing control of the impurity on each batch with an investigation if any result is above the quantification limit. In addition, the applicant committed to validate the assay by the end of Q3 2024.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The release specification includes the general tests appearance (state, colour, clarity/opalescence) and pH, test for identity (tryptic peptide mapping), purity and impurity tests for product-related variants (SE-HPLC, non-reducing CGE, iCE), test for protein content (spectroscopy), test for potency (cell-based assay), test for host cell protein (ELISA), as well as tests for safety (bacterial endotoxins and bioburden).

The active substance shelf-life specification includes the same parameters with the same acceptance criteria as the release specification, except for testing of identity, HCP, bioburden and bacterial endotoxins, which are not performed at shelf life.

The justification of the tests included in the active substance specification is based on the overall control strategy. The acceptance criteria are based on data from batches manufactured with the penultimate and commercial processes, available stability data, and according to compendial standards. This approach was considered to be acceptable. In general, the test parameters and associated acceptance criteria included in the active substance specification are found adequate to control the quality of rozanolixizumab at release and shelf-life. It is noted that the acceptance criteria for the methods: relative potency, monomer (non-reducing CGE), HMWs (SE-HPLC), main peak and APG (iCE), and HCP, have been tightened during development.

Analytical procedures

The analytical procedures used for release of rozanolixizumab active substance are a combination of compendial and non-compendial methods. Methods applied to both active substance and finished product are described in this section.

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are described in sufficient details. Information on reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial methods Appearance (colour, clarity/opalescence), pH, bioburden and bacterial endotoxins are performed in accordance with the methods described in the relevant pharmacopoeia. For bacterial endotoxins, method suitability verification has been performed for active substance and in-process samples, demonstrating endotoxin recovery in the presence of the samples.

In general, the non-compendial analytical procedures: cell-based assay, spectroscopy, tryptic peptide mapping, non-reducing CGE, SE-HPLC, iCE, and ELISA (HCP) are described in sufficient details. System suitability criteria are specified and found adequate to confirm that the methods are in control during routine testing. The methods were validated using active substance samples, which is accepted since the composition of the active substance and finished product are identical and no additional formulation or compounding steps are part of the finished product manufacturing process. When relevant, a fit-for-purpose evaluation was performed using in-process samples. In addition, the methods SE-HPLC, non-reducing CGE and iCE, were shown to be stability-indicating.

Overall, the non-compendial analytical methods have been appropriately validated for their suitability for intended use according to ICH guidelines.

Reference standards

A number of different versions of the reference standards have been used throughout the development of rozanolixizumab. During the procedure a major objection was raised as no two-tiered reference standard system is in place currently, however in response to the questions raised by CHMP, the applicant

commits to develop a two-tiered standard system by the end of Q1 2024. Qualification results of the secondary reference standards should be included in the dossier when available. This response was considered to be acceptable, and the major objection was considered to be resolved.

Release testing and extended characterisation were performed to qualify each reference standard. Qualification results are provided. The panel of tests to characterise the reference standards is found appropriate and results are generally in line with active substance batches analytical results. Characterisation of future reference standards is outlined. Overall, the qualification protocol is found acceptable. Periodic retesting of the future reference standards will be performed annually.

Batch analysis

During the pharmaceutical development of rozanolixizumab a number of different processes were used for the manufacture of nonclinical and clinical active substance material. Information on the use of the different batches has been provided, except for some commercial process batches whose use has not been assigned yet. Batches used in the pivotal clinical study were manufactured using the commercial Process.

Batch analyses data have been provided for all active substance batches produced by a number of different processes. The test methods employed and the specification for release testing of the batches were those valid at the time of testing. All batch data complied with the acceptance criteria valid at the time of testing. In addition, the commercial process active substance batches meet the acceptance criteria of the proposed commercial specification acceptance criteria which have been tightened for most of the test parameters. Overall, it is found that the batch data confirm batch-to-batch consistency and process comparability.

Container closure

The container closure system for rozanolixizumab active substance consists of sterile plastic bags, inside protective shells. The contact layer is compliant to Ph. Eur. 3.1.7 *Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations*. Tallow-derived additives are used in the manufacture of the bags. These additives, which are primarily extracted from tissues of ovine or bovine origin, are compliant to the effective version of EMA/410/01 (European Commission: *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*). The bags are compliant to Ph. Eur. 5.2.8 *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*.

The extractables studies identified components above the safety threshold/PDE (5 µg/day). A leachables study was then performed showing no safety concern.

2.4.2.4. Stability

The stability studies are designed and carried out in accordance with the ICH Q5C guideline. The proposed shelf life of rozanolixizumab active substance (36 months at ≤-60°C) is considered to be acceptable.

This shelf life is currently supported by 36 months real-time data for three consecutive batches produced by the commercial manufacturing process and stored in bags. The stability studies at the intended storage condition are ongoing and comprise additional commercial process batches, including the PPQ batches. In addition, penultimate process stability data for active substance stored in bottles are provided and considered supporting data for the commercial shelf-life specification.

The stability data gathered for penultimate and commercial process batches for the intended storage condition showed no significant change or out of specification results for all attributes, except for the

parameter monomer for two penultimate process batches. These results do not meet the proposed shelf-life specification but were considered acceptable at the time of testing as no acceptance criterion was in place for these attributes. Since no significant trend was observed for the monomer values and all results for these two batches were within the shelf-life specification, these deviations are considered acceptable.

The stability testing programme includes studies at the accelerated condition of 5°C and at the stressed conditions of 25°C/60% RH, 30°C/75% RH and 40°C/75% RH. Commercial process batches were stored in either bags or bottles in an upright position, while penultimate process batches were stored in HDPE bottles. The results obtained at the accelerated storage condition over at least 30 months for the penultimate process batches and at least 18 months for commercial process batches show similar evolutions for the two processes. The results gathered for penultimate and commercial process batches at all stressed storage conditions showed similar changes in purity profile.

Several out-of-specification results in some penultimate and commercial process batches were observed at the stressed conditions. These out of specification are sufficiently explained.

The provided post-approval stability protocol and stability commitment are acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is a solution for subcutaneous injection, supplied as a sterile preservative-free aqueous solution at a protein concentration of 140 mg/mL and a strength of 280 mg/2 mL. The solution is colourless to pale brownish yellow and clear to slightly opalescent. The finished product is formulated with L-histidine/L-histidine hydrochloride monohydrate, L-proline, and polysorbate 80. All used excipients are well-known pharmaceutical ingredients. Their quality is compliant with Ph. Eur standards, and their functions are indicated. They are confirmed to not be of human or animal origin. There are no novel excipients used in the finished product formulation. The finished product is presented in a single-dose glass vial. An overfill is applied that would allow for delivery of 2 mL/vial.

Pharmaceutical development

Components of the finished product:

The active substance consists of a nominal formulation of 140 mg/mL rozanolixizumab in L-histidine/L-histidine hydrochloride monohydrate, L-proline, and polysorbate 80 (PS80).

Formulation development:

The formulations of the initial process and the commercial process are the same. Another formulation was used solely for phase 2 trials.

Development of the liquid formulation: lead formulations were suggested by high-throughput screening and a final formulation was selected. The suitability of the final formulation was confirmed by formulation robustness testing and formulation stability tests, where the impacts of varying the formulation parameters were tested. The applicant commits to develop a quantitative assay to determine increase in free fatty acids by Q4 2024. The applicant commits to investigate adsorption of PS80 to primary product contact surfaces and provide the conclusion of the investigation by end Q4 2024. Formation of visible particles are considered out of specification results. The applicant commits to perform an investigation of the root cause, including determination of its nature, of any unexpected visible particle observed in the finished product. These commitments are considered sufficient.

Manufacturing process development:

A number of processes have been used throughout finished product development. Critical quality attribute (CQA) assessment was carried out as part of an integrated control strategy for active substance and finished product. The potential impacts on CQAs of material attributes and parameters associated with the finished product manufacturing process were evaluated using cause-and-effect analysis. Potential CPPs were identified using preliminary knowledge. Final CPPs were then selected based on severity scores, assigned using knowledge attained during process validation. The CPPs were classified into ongoing CPPs, material controls, process design controls, and validation controls. PARs are listed and justified.

The disposable polymeric materials, e.g., in filters and tubing, that contact the finished product during manufacture, have been shown to be compatible with rozanolixizumab. Light exposure of rozanolixizumab during manufacturing was assessed. It was evaluated that the amounts are sufficiently low to not impact product quality. This is acknowledged.

The finished product is filled into borosilicate clear neutral Type I glass vial, closed with a rubber stopper, sealed with an aluminium crimp seal with a plastic flip-off cap. Comprehensive extractables and leachables studies have been performed on the materials in contact with the finished product, i.e., the vial and stopper. CCIT testing was carried out during PPQ and development. All PPQ batches (and clinical batches also tested) passed. Stability results further confirm container integrity. The primary container closure system is considered safe and suitable for use with the finished product.

The finished product is supplied as a sterile, preservative-free, single-dose solution in a glass vial. During finished product manufacture, the solution is filtered through a 0.45/0.2µm filter for bioburden reduction and sterilizing grade filtration. The sterilizing filters are tested before and after use for integrity. The finished product is aseptically filled into a sterilised glass vial and sealed with a sterilised closure. Sterility and bacterial endotoxins are controlled as part of batch release testing. Container closure integrity is evaluated by CCIT as part of the stability programme. The information provided is sufficient.

Compatibility assessment found no chemical or physical incompatibility over the administration time period between rozanolixizumab and the materials proposed for use for IV and SC infusion.

2.4.3.2. Manufacture of the product and process controls

Manufacture

The finished product manufacturing process consists of nine steps: 1) thawing of active substance, 2) homogenisation and pooling, 3) bioburden reduction filtration, 4) sterile filtration, 5) aseptic vial filling, 6) stoppering/sealing, 7) visual inspection, 8) inkjet batch number printing, 9) packaging and labelling. The finished product is then stored at 2-8°C. The individual steps are described in sufficient detail and a diagram of the entire finished manufacturing process was provided.

The intended commercial batch size range for the finished product is defined. Batch formula has been provided. Excipients are not added during the finished product manufacture.

Process controls

The manufacturing process is controlled by several CPPs and IPCs. CPPs are listed along with their ranges, and IPCs are listed along with their acceptance criteria/action limits. Adequate controls on microbial quality are in place. The level of control is overall acceptable.

Process validation / verification

The manufacturing process (including process times and hold times) has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

The PPQ campaign was carried out using four consecutive batches of rozanolixizumab finished product, representing both extremes of the batch size range. Overall, the data show that the process runs consistently within the defined process parameter ranges and yields material that meets the commercial release acceptance criteria across the range of batch sizes.

Filter validation scheme and results are acceptable. Media fill runs, sterilisation validation and cleaning validation are acceptable. Mechanical shipping simulation studies were performed and confirmed the integrity of the commercial packaging components during transport. The transport validation is acceptable.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The finished product specification was established in line with ICH Q6B and monograph 2031 on monoclonal antibodies for human use. It includes tests for appearance (appearance of solution (whether product is liquid), colour, opalescence), pH, osmolality, extractable volume, PS80 concentration, relative potency by a cell-based assay, protein concentration, identity by tryptic peptide mapping, amount of intact monomer, of total LMWS and of HHL by NR-CGE, amount of HMWS by SE-HPLC, charge variants (main peak, BPG and APG by iCE), visible particles, subvisible particles (≥10 µm, ≥25 µm), sterility and amount of endotoxin.

The justification of specifications acceptance criteria was based on regulatory requirements, and confirmed by review of historical release and stability data. For the other parameters, the following were considered: formulation definition, formulation development data, historical release and stability data, and clinical exposure.

A risk assessment to evaluate the potential for formation of or contamination with N-nitrosamines in the finished product was performed in accordance with CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 (EMA/409815/2020 Rev. 1). This covered the active substance manufacturing processes, excipients in the formulation, active substance primary packaging and storage, finished product manufacturing process, packaging and storage. The assessment concluded that the risk is low, and that confirmatory testing of N-nitrosamines is therefore unnecessary. The assessment provided by the applicant is considered acceptable.

Elemental impurities were evaluated in accordance with ICH Q3D. The applicant concludes that the overall risk for potential release of elemental impurities into the finished product is low. The information on the control of elemental impurities is satisfactory.

Overall, the finished product specifications are found adequate to control the quality of the finished product at release and shelf-life. The acceptance limits are acceptable.

Analytical procedures

Since finished product and active substance formulations are the same, and no further processing is performed prior to vial fill, the methods concluded to be validated for active substance testing can be considered to also be validated for finished product testing. The finished product section therefore only addresses the non-compendial methods specific to finished product. The analytical methods used for testing of the finished product are considered suitable for their purposes and appropriately validated in accordance with ICH guidelines.

Reference standards

Reference standards for stability testing and release testing of the finished product are the same as used for the rozanolixizumab active substance. No additional reference standards are used for testing of the finished product.

Batch analysis

Batch analysis data are presented for development batches, representing each finished product process. All batches met the specifications in place at the time of release, and the PPQ batches demonstrate manufacturing consistency.

Container closure

The container closure system for the finished product is a borosilicate clear neutral Type I glass vial closed with a rubber stopper and sealed with an aluminium crimp seal with a plastic flip-off cap. The vial complies with Ph. Eur. 3.2.1 "Glass Containers for Pharmaceutical use" and the rubber stopper complies with Ph. Eur, 3.2.9 "Rubber closures for containers for aqueous parenteral preparations, for parenteral use". The container closure system is considered adequately described.

2.4.3.4. Stability of the product

Based on available stability data, the shelf life and storage conditions as stated in the SmPC (24 months in refrigerator (2 °C – 8 °C)) are acceptable. The product should not be frozen, and the vial should be protected from light.

The stability programme is carried out in accordance with ICH Q1A and ICH Q5C. Testing has been performed at appropriate intervals using validated stability-indicating methods on 3 primary batches from the commercial process and a number of supportive batches (4 PPQ batches, a number of batches using the initial finished product Process based on the penultimate and commercial active substance Processes).

For the primary batches, testing at the long-term condition (5°C±3°C) has been performed for the full 24-month duration of the proposed shelf-life. For the long-term conditions, vials have been placed in both upright and inverted position, and one primary batch also in the horizontal position. The primary packaging is the same as the one proposed for routine storage. In addition, the 12-month accelerated (25°C±2°C /60%±5% RH accelerated) and the 6-month stressed studies (30°C±2°C /75%±5% RH and 40°C±2°C /75%±5% RH) are completed. The PPQ batches have been tested for 12 months long-term and the stressed studies are completed. The supportive process batches have been tested for up to 48 months at the long-term condition, and the accelerated and stressed studies are completed. No claim is made that the product can be stored for a period of time at 25°C before opening.

Photostability studies were performed in accordance with ICH Q1B for a primary and a supportive batch. The results from the study show that the sample is indeed photosensitive. However, it was demonstrated that the secondary packaging provides sufficient protection. Two thermal cycling studies were performed.

The applicant has provided a post-approval stability protocol for the rozanolixizumab finished product, which is accepted.

2.4.3.5. Adventitious agents

Apart from the CHO-derived production cell line no material from animal/human origin has been used in the manufacture of rozanolixizumab active substance and finished product. It is informed that tallow derivatives used in the CryoTube screw caps and in the bags for active substance storage have been

manufactured with processing conditions that meet the criteria defined in EMA/410/01 (European Commission: *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*). All raw materials and all excipients are tested for bacterial endotoxins, excipients are further tested for bioburden. The active substance is tested for absence of fungi and bacteria and bacterial endotoxins at several steps during manufacture and at release. Finished product is tested for bioburden during manufacture as in-process control, and for sterility and bacterial endotoxins at release. Overall, the product is considered safe with regard to non-viral adventitious agents.

Cell banks have been tested for non-viral and viral adventitious agents according to ICH Q5A and ICH Q5D. MCB, WCB and PPCB were shown to be free of detectable bacterial, fungal and mycoplasma contamination. The MCB was also tested negative for mycobacteria. The MCB and PPCB were tested for viral safety including general *in vitro* assay for adventitious viruses, *in vivo* assay for inapparent viruses (adult mice, suckling mice and embryonated eggs), reverse transcriptase activity, detection of retroviruses by S^+L^- focus detection of virus-like particles and PCR assay for murine minute virus. In addition, the MCB was found negative for murine virus by the mouse antibody production test and negative for hamster virus by the hamster antibody production test. Porcine trypsin and bovine serum were used early in the cell line development in the preparation of the host cell bank. The MCB was shown to be free of porcine and bovine viruses. Since there was no further exposure to materials of animal origin, it is accepted that the WCB and PPCB were not tested for bovine and porcine adventitious viruses. A reduced panel of tests (*in vitro* and *in vivo* adventitious tests) was conducted on the WCB, this is found acceptable according to current guideline. No non-viral nor viral adventitious agents were detected. No endogenous retroviruses were detected except for A-type retrovirus-like particles which are known to be present in cells of CHO origin. The cell banks are therefore considered safe for use in the manufacture of rozanolixizumab with regard to the risk of viral and non-viral adventitious agents and endogenous retroviruses.

The viral clearance capacity of the rozanolixizumab active substance purification process was evaluated by conducting virus clearance studies using qualified scale down models in accordance with ICH Q5A. The scale down procedure is considered acceptable and the scale down models are representative of the commercial scale. CPPs having the potential to impact viral clearance were identified.

The selected model viruses represent a wide range of particle size, genome type, and degree of resistance to chemical treatments as required by ICH Q5A.

The virus clearance obtained across the process steps investigated in the virus clearance validation studies is considered acceptable.

End of resin lifetime study was performed using feed material samples from the commercial Process with the four model viruses. In addition, the efficiency of the resin sanitisation procedures for avoiding virus carryover was evaluated.

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of adventitious (and endogenous) agents in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the rozanolixizumab purification process. In conclusion, rozanolixizumab is considered safe for commercial purposes with regard to risk of contamination with adventitious non-viral or viral agents or with endogenous viruses.

2.4.3.6. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

During the procedure a major objection was raised on the reference standard as there is no primary reference standard used to qualify working standards. In response the applicant commits to put in place a two-tiered reference standard system by the end of Q1 2024. This was accepted and the major objection was considered to be resolved.

During the procedure a major objection was raised requesting that the applicant should further substantiate the new active substance claim. In response the applicant provided results from database searches comparing the sequence of rozanolixizumab to the sequences of all available antibodies approved in the EU. The major objection was considered to be resolved, and rozanolixizumab is considered to be a new active substance.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development. For details refer to section 2.4.6.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation (which the applicant has committed to address):

1. The applicant commits to develop a two-tiered reference standard system by the end of Q1 2024. The dossier should be updated with the qualification results of the secondary standard when available.
2. The applicant commits to generate data on commercial scale active substance batches to support and confirm hold times based on bioburden and endotoxin levels present in each active substance intermediate. The data will be generated during the next active substance manufacturing campaign which is currently scheduled for Q2 2024. The data (including defined hold times) will be evaluated and provided to the agency by end of Q3 2024. The agency will be notified accordingly in the event of changes in the manufacturing schedule for the next active substance manufacturing campaign.
3. The applicant commits to introduce the determination of the residual level of an impurity as an IPC with a limit corresponding to the quantification limit of the method used for testing samples at this step. The IPC will be implemented with the next manufacturing campaign. Until this IPC will be put in place, the control of the IPC will be done on each batch. Any result above the quantification limit will be recorded and investigated.

4. The applicant commits to validate the method used for an in-process impurity as IPC by the end of Q3 2024.
5. The applicant commits to develop a quantitative assay to determine whether there is an increase in free fatty acids in stability finished product samples by Q4 2024.
6. The applicant commits to investigate adsorption of PS80 to primary product contact surfaces and provide the conclusion of the investigation by end Q4 2024.
7. The applicant commits to perform an investigation of the root cause, including determination of its nature, of any unexpected visible particle observed in the finished product.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical development programme consists of a comprehensive evaluation of the PD, PK, and toxicology of rozanolixizumab and supports the treatment of MG and other autoimmune diseases. The programme is consistent with the requirements of the International Council for Harmonisation (ICH) guidelines ICH M3(R2) and ICH S6(R1). The non-pivotal and pivotal repeat dose toxicology studies in cynomolgus monkey, that include safety pharmacology and local tolerance assessments, and the tissue cross-reactivity study assessing compound binding to a comprehensive set of cynomolgus monkey and human tissues were carried out in compliance with both local and Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP) and in countries that are part of the OECD Mutual Acceptance of Data programme. The target binding and affinity, the functional activity and the PD activity of rozanolixizumab in reducing the plasma levels of IgG were characterised in a number of *in vitro* and *in vivo* studies, in transgenic mouse models and in the cynomolgus monkey.

A comprehensive toxicology programme, including safety pharmacology endpoints, has been completed in the cynomolgus monkey to support IV (intravenous) and SC (subcutaneous) administration of rozanolixizumab in clinical trials. This included GLP-compliant general toxicology studies of up to 26-weeks duration where animals received IV or SC doses of up to 150 mg/kg rozanolixizumab every three days, an enhanced pre- and post-natal development study (ePPND), and tissue cross-reactivity studies using human and cynomolgus monkey tissues.

In addition, a 1-week toxicology study at a dose level of 150 mg/kg iv was initiated in the rhesus monkey in order to investigate whether the acute adverse events (AEs) observed in the first-in human (FIH) study (gastrointestinal [GI] symptoms, headache), and absent in cynomolgus monkey with a large safety margin, could be detected in this strain.

2.5.2. Pharmacology

The FcRn is composed of the FcRn α chain in association with β2-microglobulin, and the receptor is expressed on a number of different cell types, notably endothelial cells, epithelial cells, and haematopoietic cells such as monocytes/macrophages. Rozanolixizumab (synonym UCB7665) is a humanised mAb of the immunoglobulin G (IgG)4 class, which specifically binds to the FcRn α chain and is currently being developed by the applicant for the treatment of gMG in adult patients who are AChR or anti-MuSK antibody positive.

Rozanolixizumab is designed to bind to the FcRn receptor at both acidic and neutral pH preventing salvage of IgG and thereby increasing its clearance by lysosomal degradation. In this way

rozanolixizumab is believed to also increase the clearance of pathogenic IgG autoantibodies in patients of autoimmune diseases such as gMG.

2.5.2.1. Primary pharmacodynamic studies

Binding and affinity studies

Biacore affinity experiments demonstrated similar affinity of rozanolixizumab to FcRn of human and cynomolgus origin with KDs of 55pM at pH 7.4 (range 27 to 117) and 44pM at Ph 6.0 (range 22 to 102) for human FcRn and KDs of 57pM at Ph 7.4 (range 43-69) and 42pM at Ph 6.0 (range 12 to 84) for cynomolgus monkey. Affinity (KDs) for rozanolixizumab for mouse and rat FcRn was much weaker (nanomolar range) and binding to rabbit FcRn was not observed at all.

To demonstrate affinity in a more physiological environment of a cell membrane, affinity of fluorescently labelled rozanolixizumab to FcRn in a cell-based assay of flow cytometry was carried out using buffers of neutral (7.4) and acidic pH (6.0). The potency was similar between the two pHs for both species. Although the potency of rozanolixizumab was slightly poorer to FcRn from cynomolgus monkey (KD = 1.03 – 1.1 nM) as compared to human (KD = 0.36-0.43 nM), these data support the use of cynomolgus monkey as non-clinical testing species.

Mechanism of action *in vitro*

In a functional *in vitro* assay in FcRn (human or cynomolgus monkey) transfected Madin-Darby canine kidney cells in 96 well plates, the ability of rozanolixizumab to inhibit biotinylated IgG recycling was evaluated by measuring IgG in both intracellular lysate and extracellular levels in incubate of cells transfected with the human FcRN. The ability of rozanolixizumab to inhibit transcytosis of biotinylated human IgG from the apical to the basolateral chamber of a confluent layer of FcRn transfected cells was evaluated by analysing for biotinylated IgG in the basolateral chamber of 24 well transwell plates, but only for human FcRn. 50% inhibitory concentration (IC_{50}) values were in the range of 0.4 (human) to 1.1 nM (cynomolgus monkey) for which the data on recycling indicate a factor of 2 better potency on the human FcRn. In IgG recycling experiments using Cynomolgus monkey FcRn-transfected cells, the IC_{50} value was 0.98nM.

Any slight decrease in affinity in monkey versus human would be compensated for by the high doses of rozanolixizumab used both in the non-clinical pharmacology and toxicology programme with cynomolgus monkeys.

Mechanism of action *in vivo*

The ability of rozanolixizumab to accelerate clearance of human IgG (hIgG) in a human FcRn-transgenic (hFcRn Tg) mouse was evaluated in one study.

Human IgG was administered IV to hFcRn Tg mice on day 1. Treatment with rozanolixizumab began on day 2. Mice received a single dose of rozanolixizumab at 10, 30 or 100 mg/kg as either an IgG1 or IgG4 format. An initial blood sample was taken from a peripheral vessel prior to the commencement of antibody dosing. Serial bleeds were then taken at multiple time points post antibody dosing. Levels of hIgG, albumin and rozanolixizumab were quantified using liquid chromatography – tandem mass spectrometry/mass spectrometry (LC-MS/MS).

Both the middle and high dose almost abolished the administered human IgG (500 mg/kg) by 192 hours after administration to only 5-7% of initial levels of hIgG left. This study was supported with exposure of rozanolixizumab. However, data was too sparse to calculate PK parameters.

Maximum dose of rozanolixizumab in patients is 560 mg/50 kg = 11.2 mg/kg. Human equivalent dose (HED) of 100 mg/kg in a mouse is 100/12.3[#] = 8.1 mg/kg, hence the highest dose in this study corresponds to the highest recommended dose in patients (#: FDA: Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005). However, geometric mean maximum plasma concentration observed (C_{max}) in Caucasians healthy volunteers was only 19.74 µg/Ml after a single dose of 10 mg/kg SC, much lower than the maximum plasma concentration in mouse of 713 µg/Ml, 8 hours after administration. Nevertheless, maximum decrease in IgG was observed in all subjects on Day 10 with a mean decrease of 50.76%. However, comparing effective plasma concentrations between an artificial system such as the transgenic mouse expressing the human FcRn receptor and patients is complex.

The ability of a mouse surrogate (4470) of rozanolixizumab to increase clearance of IgG was evaluated in a mouse disease model of immune thrombocytopenia (ITP). At the same IV dose levels as in the study in the hFcRn transgene mouse model, the mouse surrogate antibody against mouse FcRn was demonstrated to alleviate the decrease in platelet numbers after administration of an antibody against mouse CD41 delivered by an Alzet minipump, which induced phagocytosis of platelets. The treatment was efficient both as a partly prophylactic treatment regime (Day 0, 2 and 4) and as a pure treatment regime (Day 3 and 5) at 30 mg/kg. The dose of 100 mg/kg administered on Day 3 and 5 was just as effective in normalizing platelet levels on Day 6 as IV immunoglobulin treatment 1000 mg/kg administered on day 3 only.

The efficacy of a surrogate anti-mouse FcRn mAb (4470) was explored in a mouse model which has features of both encephalomyelitis and optic neuritis, which are also associated with oligodendrocyte glycoprotein-associated disease (MOG-AD) in human patients.

Treatment with 4470 demonstrated a reduction of clinical score relative to an isotype control mAb (101.4) over the course of the disease that was statistically significant, and this was accompanied by statistically significant reductions in both demyelination and macrophage infiltration in the spinal cord tissue, assessed histologically. Additionally, visual acuity (assessed by optokinetic reflex, OKR) was preserved in 4470-treated mice relative to mice treated with control antibody when assessed at baseline and at the end of the study, and this was also statistically significant.

2.5.2.2. Secondary pharmacodynamic studies

A cell microarray screening study on >4500 human plasma proteins expressed in HEK-293 cells was used to evaluate any potential off-target activity of rozanolixizumab. Of the 20 initial hits, including FcRn itself, two other hits were investigated further for relevance. One hit corresponding to c-CBL (E3-ubiquitin ligase) was strong but was not considered clinically relevant since it is an intracellular target and not accessible to rozanolixizumab from the extracellular compartment. The protein was accessible to rozanolixizumab in this study due to the fixation process. The second hit corresponded to CD99L2 and was weak. It was considered an artefact based on sequence analyses. Hence, based on the Retrogenix array analysis, rozanolixizumab is specific for FcRn.

2.5.2.3. Safety pharmacology programme

Evaluation of rozanolixizumab potential impact on the cardiovascular (CV), central nervous and respiratory system was included in the 4-week and the 13-week repeat-dose toxicity studies.

Cardiovascular system

In the 4-week study, the CV observations were performed twice during pre-dose phase in temporarily restrained animals, Weeks 1 and 4 of dosing phase and in the last week of the recovery phase.

In the 13-week study, the CV observations were performed once during pre-dose phase and Weeks 3 and 12 of dosing phase (excluding Group 4). For Group 4 only: Weeks 6 and 10 of dosing phase.

Timing of CV observations was 2 hours ±15 minutes post dose in both studies.

No dose-related changes were observed for electrocardiogram (ECG), the QRS complex duration, PR interval, RR interval, QT interval or heart rate in any phase or study. When changes occurred, these were either consistent with similar findings in animals during the pre-dose phase or also observed in animals of the control group and therefore not considered toxicologically relevant.

It should be noted that there is no information on pre-study training in being restrained during safety pharmacology data collection in the study report.

Respiratory system

In connection with the CV evaluation, observations regarding the respiratory system were performed by counting respiratory phases and manual observation of respiratory depth in both the 4-and the 13-week study. Since no effects or changes were observed during the dosing phase, this evaluation was omitted in the recovery phases of both studies.

CNS

Neurobehavioral observations were performed as a functional observational battery adapted for monkeys. This was taking place along with determination of body temperature 5 days prior to the dosing phase and on Day 24 of the dosing phase in the 4-week study. Some males showed defensive aggression only during the pre-dose phase or during all the study. Since no remarkable changes were observed, this test was not repeated during the recovery phase.

For the 13-week study, this was performed once during pre-dose phase and weeks 3 and 12 of dosing phase. Moreover, it was inadvertently performed at the end of the recovery phase for the female study animals. Some females of all treatment groups including controls showed defensive aggression during the pre-dose phase and/or during the study, which is considered a background finding in this species. In addition, one Group 3 male animal showed stereotypy on Days 18 and 83, while one Group 5 female animal was hypervigilant on Day 78. Both findings were considered incidental. Since these observations were in single animals, this is agreed.

2.5.2.4. Pharmacodynamic drug interactions

No known interaction on receptor level is known for rozanolixizumab except for the intentional target of the FcRn receptor. The cell microarray screening study did not reveal any off-target activity.

It should, however, be noted that inhibition of FcRn will increase clearance for concomitant treatment with other IgG-based products.

2.5.3. Pharmacokinetics

Methods of analysis

Two ways of quantitative measures of exposure (free and total rozanolixizumab) and one for pharmacologic effects (total IgG) were performed for rozanolixizumab in the general toxicity studies.

Free rozanolixizumab concentrations were determined by immunoassay (MSD), and total rozanolixizumab concentrations (free and ADA-bound UCB7665) were determined using LC-MS/MS of trypsin digested free and antidrug-antibody-bound rozanolixizumab.

In parallel, total endogenous plasma IgG levels, a measure of the PD activity of UCB7665 was determined also using LC-MS/MS. The presence of anti-rozanolixizumab antibodies (ADA) was measured by immunoassay.

Methods for determining exposure as free and total were validated to GLP and fulfilled the incurred sample reproducibility according to guidelines as determined in the 4-week study.

Mean free rozanolixizumab which is accessible to the FcRn receptor make the basis for calculation of safety margins to patient exposure.

In the 4-week study, mean maximum concentrations of, and exposure to, free UCB7665 were generally greater than that of total UCB7665, which seem counterintuitive.

In the 13-week study, mean maximum concentrations of, and exposure to, free-UCB7665 were generally similar to those of total-UCB7665. The similarity in concentrations suggested that UCB7665 was effectively free and not held in immunocomplexes.

The ratio of total and free rozanolixizumab changed from study to study were the free was higher than total in the 4-week study, similar in the 13-week study and lower in the 26-week study. The apparent study dependent ratio between free and total rozanolixizumab, where the free amount was higher than total amount in the 4-week study, similar in the 13-week study and lower in the 26-week study, could be to be attributed to analytical method variability, but most importantly interindividual variability in the monkeys themselves. Moreover, the incidence and amounts of ADA (binding and/or neutralising) typically increase with time, gaining opportunity to impact exposure of free rozanolixizumab.

Rozanolixizumab was typically reported as µg/mL and rarely as ng/mL.

The ADA assay, which is semiquantitative (relative to control), was also validated to GLP and appeared fit for purpose. The control material used in the assay is a purified anti-UCB0660 response from cynomolgus monkey plasma. UCB0660 is a pegylated Fab with the same idiotype as rozanolixizumab, which is the full-length IgG4. Drug tolerance was determined to be as follows: 30 ng/Ml positive control is BLQ in the presence of 1 µg/mL rozanolixizumab. 30 ng/mL positive control is in range in presence of 250 ng/mL. 600 ng/Ml positive control is in range in the presence of 1 µg/mL of rozanolixizumab. This method was further optimised with regard to drug tolerance prior to the use in the ePPND study and validated again. Then, 1000 ng/mL of positive control was tolerant up to 1 mg/mL of rozanolixizumab, 100 ng/mL of positive control was tolerant up to 250 µg/mL of rozanolixizumab and 27.5 ng/mL of positive control was tolerant up to 20 µg/mL of rozanolixizumab.

Absorption

Primary and secondary PK parameters was presented for monkeys and humans. The values were derived from PKPD mixed-effects modelling. Moreover, an accepted publication on PK-PD modelling of the anti-FcRn mAb rozanolixizumab: Translation from preclinical stages to the clinic was submitted in support of the presented PK parameters (Lledo-Garcia et al, 2022). Finally, model-derived human exposure was used to calculate margins of safety, when compared with non-compartmentally derived exposure of free rozanolixizumab in monkeys in the toxicology studies. Margin of safety is in the range of 36-228. See Tables 1 – 3.

Table 1: Comparison of PK parameters in cynomolgus monkeys and humans

PK Parameter	Cynomolgus Monkey		Humans	
	Estimate	Source	Estimate	Source
F	55-65%	Module 2.6.4 Table 8-3 and Table 8-4	67%	CL0460 Report Table 4
CL	0.071L/day	Lledo-Garcia et al. 2022	1.11 L/day	CL0460 Report Table 4
V	0.11L	Lledo-Garcia et al. 2022	3.0L for <10mg/kg and 3.5L for ≥10mg/kg	Module 2.7.2, Section 2.4.1
CL/F	NC		0.89L/day	CL0534 Report Table 14
V/F	NC		6.6L	CL0534 Report Table 14
T_{max}	24h	Module 2.6.5 Table 4	2 days	Module 2.7.2 section 3.1.1

NC: Not calculated

Table 2: Human exposures considered for calculation of the safety margins

Dosing regimen	$C_{max,ss}$ (µg/mL)	$AUC_{tau,ss}$ (µg*day/mL)
≈7mg/kg	17.45	60.90
≈10mg/kg	45.90	207.5

AUC area under the curve; C_{max}: maximum concentration
For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈7mg/Kg: 35 to <50kg: 280mg, 50 to <70kg: 420mg, 70 to <100kg: 560mg, ≥100kg: 840mg. For ≈10mg/Kg: 35 to <50kg: 420mg, 50 to < 70kg: 560mg, 70 to <100kg: 840mg, ≥100kg: 1120mg).
Note: Six weekly doses were simulated for each dosing regimen.

Table 3: Safety margin relative to the predicted PK in the gMG population

nonclinical study	Bioanalytical method	dosing regimen	Cmax (µg/mL)	human dose	MOS on Cmax	AUC0-72h (µg*day/mL)	AUC corrected for 7 days (µg*day/mL)	human dose	MOS on AUC
4-week toxicity study NCD2447	free	150 sc every 3 days	1850			3560	8308		
				≈7mg/kg	106			≈7mg/kg	136
				≈10mg/kg	40			≈10mg/kg	40
		150 iv every 3 days	5955			5958	13903		
				≈7mg/kg	341			≈7mg/kg	228
				≈10mg/kg	130			≈10mg/kg	67
13-week toxicity study NCD2448	free	150 sc every 3 days	1735			3780	8820		
				≈7mg/kg	99			≈7mg/kg	145
				≈10mg/kg	38			≈10mg/kg	43
		150 iv every 3 days	4870			5370	12530		
				≈7mg/kg	279			≈7mg/kg	206
				≈10mg/kg	106			≈10mg/kg	60
26-week toxicity study NCD2553	free	150 sc every 3 days	2370			5458	12736		
				≈7mg/kg	136			≈7mg/kg	209
				≈10mg/kg	52			≈10mg/kg	61
ePPND study NCD3001	free	150 sc every 3 days	1500			3180	7420		
				≈7mg/kg	86			≈7mg/kg	122
				≈10mg/kg	33			≈10mg/kg	36

AUC area under the curve; C_{max}: maximum concentration; IV: intravenous; MOS: margin of safety; SC: subcutaneous.

Distribution

Distribution studies are normally not performed for mAb, since studies of distribution of radiolabelled antibodies are difficult to interpret (ICH S6). However, in the ePPND study, infants of mothers dosed 150 mg/kg every 3 days had detectable rozanolixizumab in plasma on postnatal day (PND)-1, but not on PND-7. Hence, transfer across placenta through pregnancy appear plausible, although low.

Metabolism

According to ICH S6, the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood. Classical biotransformation studies as performed for pharmaceuticals are not needed.

Excretion

Excretion studies are not necessary for mAb, since they are typically degraded to small peptides and individual amino-acid and in incorporated in the catabolic systems in the body. Moreover, rozanolixizumab is a mAb comprising native non-modified amino acids, does not contain any chemical linkers or chelators.

Pharmacokinetic drug interactions

No drug-drug interaction (DDI) studies were performed with rozanolixizumab.

Single dose PK

Single dose PK is discussed under absorption and under each of the repeat-dose toxicokinetic (TK) studies.

Repeat dose PK

Explorative PK/PD study

A complex PKPD study was performed in nonhuman primates (NHP), testing several different dosing regimens to inform on an optimal dosing regimen in patients. The study was conducted in 2016. Quantitative determination was performed for free and total rozanolixizumab and total IgG along with other biomarker endpoints related to immunosuppression after mycophenolate mofetil treatment. A descriptive discussion of the most important data was presented in the PK summary demonstrating rozanolixizumab increasing clearance of IgG in a dose- and dosing regimen-dependent manner showing the delay between time for maximal plasma concentration and nadir of IgG. The greatest decrease in circulating mean IgG levels was observed at -83%, corresponding to treatment conditions of a single IV dose given at 30 mg/kg (loading) followed by a daily maintenance dose given at 5 mg/kg for 41 Days. The maximum recommended dosing regime is 560 mg/week in patients corresponding to ~ 10 mg/kg/week. HED of 30 mg/kg = 30/3.1* = 9.7 mg/kg (*: Monkey BSA conversion factor. Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA. 2005) showing that non-clinical data supports the clinical effect at this dosing regimen.

A publication (Lledo-Garcia, 2022) was submitted describing the development of the semi-mechanistic human PKPD model using initial estimates derived from the monkey PKPD model using the data from the explorative PKPD study, *in vitro* and literature values. The model was refined using single dose FIH data. The choice of structural model and reasoning for initial estimates were well described. Moreover, the choice of a relatively simple model (target mediated drug disposition (TMDD) with indirect response) for describing a very complex system is supported by the principle of parsimony and omission of over-parameterisation.

The applicant explains that the model on which the new flat dosing regimen is based was further populated and refined with clinical data as they became available. The human PKPD model is assessed in the clinical section.

Basic toxicology study in rhesus monkeys

A so-called basic toxicology study was performed in rhesus monkeys. Three male Rhesus monkeys were dosed IV on study days 1 and 4 with 150 mg/kg of rozanolixizumab. Eight samples were taken for bioanalysis over the next 144 hours, however, no formal PK calculations were performed. The decline in plasma concentrations were fast and exponential with no signs of TMDD, however, this could be due to the sparse sampling and/or the high dose. No comparison to cynomolgus monkey or human were performed.

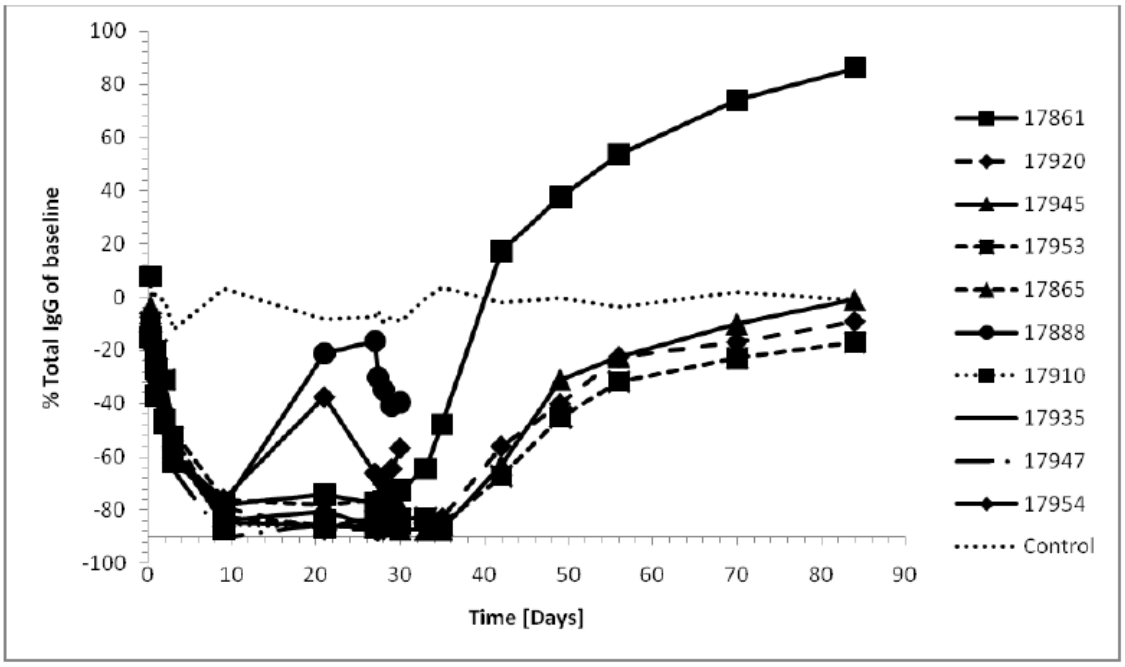
A 4-week repeat-dose toxicity study

In this 4-week repeat-dose toxicity study, rozanolixizumab was dosed either as 0, 50 or 150 mg/kg SC every 3 days or 150 mg/kg IV every 3 day (N=3/sex). 2 animals of each sex were allocated to recovery groups in the control and the 150 mg/kg groups. Blood was collected for bioanalysis of free and total UCB7665, total IgG and ADA twice during the predose phase, predose as well as 10 minutes postdose (only IV group), 1 and 4 hours postdose (free rozanolixizumab for SC low and high dose only), 8 and 24 hours postdose, 36 hours postdose (free rozanolixizumab for SC low and high dose only), as well as 48 hours postdose on Days 1 and 28. Furthermore sampling was performed predose on Days 4, 10, and 22, as well as 72 hours postdose on Day 28. During the recovery phase, blood samples were taken on Days 34, 36, 43, 50, 57, 71, and 85.

After SC administration, time for maximal plasma concentration was achieved after 48 hours. Terminal half-life was in the range of 26 to 68 hours on Day 1 and 15 to 30 hours on Day 28, indicating increased clearance on the last day of the study, presumably due to ADA.

No significant difference in exposure between genders was observed. SC bioavailability was in the vicinity of 60% on both Day 1 and Day 28 when comparing area under the plasma concentration versus time curve from time 0 to 72 hours ($AUC_{0\text{-}72h}$) at the dose of 150 mg/kg dosed by the SC with the IV route. It appears that the bioavailability is much lower in humans at the doses of 7 mg/kg and below. It is acknowledged that the dose levels between human and monkey is substantially different. The apparent much lower bioavailability in human as compared to monkey at a single IV dose of 7 mg/kg when using data from Phase 1 study UP0018 was explained by the lack of ability to calculate area under the plasma concentration versus time curve from time 0 to infinite (AUC_{inf}), hence being a PK calculation technicality. The current population PKPD (Pop-PKPD) model predicts similar bioavailability in humans as in monkeys. As expected, some animals were found positive for ADAs, especially in the low dose group, in which loss of pharmacological effect associated with decreased levels of rozanolixizumab correlated with the presence of ADAs. However, this was not always the case in the high dose groups, although substantial variability in exposure and IgG was observed on Day 28 for all three active dose groups. In the group of 150 mg/kg SC one animal lost effect on IgG around Day 30 and thereafter overshooting the % IgG to 90% over baseline. The cause of IgG overshooting in one male monkey after stopping treatment with rozanolixizumab is ascribed to a swollen food and not using his leg for several weeks. Clinical chemistry parameters and necropsy confirmed the severe local and also to some extent systemic inflammation in this animal. The explanation for IgG overshooting in this animal is accepted and the observation is most likely not clinically relevant. See Figure 1 below.

Figure 1: Percent change from baseline total IgG, 150mg/kg SC every three days.



A 13-week repeat-dose toxicity study

Sampling for toxicokinetics and total IgG in the 13-weeks repeat-dose toxicity study was designed in a similar way to the 4-weeks study. Besides the 0 mg/kg SC (N=3/sex), 50 mg/kg SC, 150 mg/kg SC and 150 mg/kg IV every 3 days (N=4/sex), a group receiving intermittent dosing (2 doses, 3 days apart) on three occasions in week 1, week 6 and week 10 was included in this study (N=4/sex). All groups, except the low dose group included 2 animals per sex for evaluation of recovery.

Rozanolixizumab did not accumulate during the study. This would have been expected, if not for the substantial development of ADAs in most animals over time. There was no sex difference in exposure at any dose on Day 1 and it was the same picture over time for the high dose groups, however in the low dose group, the females lost exposure determined as free rozanolixizumab, but not if determined as total correlating to extensive development of ADAs.

Bioavailability varied in the range of 40 to 77% on Day 1 being lowest in females at the low dose of 50 mg/kg SC.

Dose proportionality between the SC dosing groups was observed with a tendency to higher than linear in both males and females on Day 1, however the extent of supra–dose-proportionality increased already on the second sampling occasion on Day 37, especially for free rozanolixizumab in the female animals, again correlating with potential impact of ADA on PK. Continuous dosing thereafter somewhat restored the exposure and effect on IgG presumably carried by data from one female monkey in the 150 mg/kg SC every 3 days group.

While development of ADA caused considerable variability in free rozanolixizumab and also in total IgG over time, a sufficient number of animals retained exposure to the end of the study. $AUC_{0\text{-}72h}$ (free rozanolixizumab of 3780 and 5370 µg/mL*h was maintained in the 150 mg/kg SC and IV dose groups, respectively on Day 88.

It should also be noted that presence of ADAs not always correlated with loss of effect. Hence, ADAs are not considered to have hampered the integrity of the study and the conclusions drawn in terms of safety and toxicological end points.

A 26-weeks repeat-dose toxicity study

In the final pivotal repeat-dose toxicity study, only one active dose-level (150 mg/kg every 3 days for 26 weeks) was included and compared to a control group. As female animals appeared more prone to ADA development and loss of efficacy 8 females and 6 males were included in the study. One female completely lost efficacy and was euthanised in week 9. One female demonstrated consistent reduction in exposure, however maintained efficacy. Thereafter, two more female monkeys were initiated on treatment to be included in the study. Overall, it appears that female monkeys are more prone to react to rozanolixizumab with immunogenicity which hamper efficacy than males.

In this study, the exposure ratio between male and female approached a factor of two in week 26 for total and in week 13 for free rozanolixizumab correlating with a slightly higher incidence of ADAs in female animals. Nevertheless, it was chosen to show exposure as combined. This is considered acceptable, and the same approach was used in the previous studies, where no significant sex differences were noted.

A doubling of exposure was observed from Week 1 to Week 13. There was no additional accumulation between week 13 and week 26 in the group, demonstrating that exposures were at steady state in week 13 as well as at week 26. Sufficient exposure was therefore demonstrated through the time course of the study. Moreover, efficacy was also maintained; Overall, the mean group nadir was a reduction of endogenous IgG to 18% of pre-dose baseline levels observed after the final dose.

ePPND study

An ePPND study was conducted using 57 female monkeys (19 females/group) administered vehicle or 50, or 150 mg/kg rozanolixizumab (Groups 1, 2, and 3). Vehicle or rozanolixizumab were administered SC once every 3 days, starting on Gestation Day 20 (GD20) until birth. Blood samples were collected from maternal animals for TK analysis, ADA analysis, and endogenous IgG levels during gestation and in the lactation period (until PND180). During maturation of the offspring, blood samples were collected for TK analysis, ADA analysis, and IgG.

The mothers developed ADA against rozanolixizumab over time instigating high variability in exposure and response in the low dose group, the high dose group-maintained exposure through gestation and even showed some accumulation of rozanolixizumab towards the end of the study.

Rozanolixizumab could not be detected in infants at birth in the low dose group, but in some infants (6/19) in the high dose group. At PND7, no rozanolixizumab could be detected in any infant. The ratio to maternal rozanolixizumab was estimated to be 63 times higher in the mothers than in infants on PND1.

Intrapartum transfer of IgG across the placenta from mother to foetus affords immune protection to the newborn, to compensate for having a naive and immature immune system. IgG transfer increases throughout gestation as the foetus and placenta mature and grow. *In vitro* cellular and human placenta transport studies show that IgG transfer is dependent on FcRn expression in apically located vesicles within syncytiotrophoblasts, which are the placental interface to maternal circulation. At birth, the mother provides a full complement of IgG (including antibodies to environmental pathogens that the mother may have encountered) to the neonate, who normally has a serum IgG concentration comparable to if not slightly higher than the mothers. Although the foetus and neonate have been shown to be capable of making specific IgM and IgG antibody if challenged, slow production of IgG results in neonatal IgG levels reaching a nadir at age 3 to 4 months before gradually increasing (Patel 2020). This nadir was also demonstrated in the infants from total IgG profiles obtained from birth until PND180 in the vehicle group, whereas these profiles were skewed and showed high variability most likely depending on whether their mothers had been exposed to rozanolixizumab, ADAs or both.

Although it seems that there is no consistent correlation between ADA responses and rozanolixizumab dose/exposure but in this ePPND study in cynomolgus monkeys, it seemed that higher ADA responses are seen with lower doses. Additionally, there is a tendency of a similar phenomenon both in the 4-week and 13-week toxicology studies. The potential explanation that high drug levels might influence the ADA assay is plausible and can support the observations. It is also acceptable that for the toxicology studies, the effect of the drug on the ADA assay is not systematically determined, especially considering the note, that evaluation of the immunogenicity in clinical studies has demonstrated a low impact on pharmacodynamics and no impact on efficacy or safety.

In study NCD3001 in the control (vehicle only) group, one maternal animal (Animal P0016) exhibited a detectable, persistent, albeit low concentration of UCB7665 in its blood samples, also predose GD 20, and this control animal and its infant also had a low ADA response. It was suggested that a potential interference of this specific animal's plasma was present in the used bioanalytical assay. However, the measurable ADA signal, although very low (mostly below the cut point) and delayed, also raise the possibility of an inadvertent exposure to rozanolixizumab which, in absence of evidence of mis-dosing, certainly is one of the probable explanations. More importantly, this specific result in a single animal seems to have no influence on the integrity of the whole study.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No stand-alone single-dose toxicity studies have been performed with rozanolixizumab. The single-dose and multiple-dose PK/PD study in cynomolgus monkey also included a limited number of safety endpoints. Plasma IgG concentrations reduced in a dose-dependent manner with a maximum reduction of ~75% from predose levels after administration of a single dose of 30 mg/kg (the highest dose).

2.5.4.2. Repeat dose toxicity

Only NHPs were found to be a relevant pharmacologically active species. Hence, the repeat dose toxicity studies are performed in one species only primarily the cynomolgus monkey, but an exploratory toxicity study in rhesus monkey was also undertaken in order to establish if this NHP would express the GI and CNS AEs observed in the early clinical trials.

In the 4 week repeat dose study the following parameters were evaluated following administration of rozanolixizumab at 50 mg/kg (SC) or 150 mg/kg (SC or IV) every 3 days; clinical signs, body weight, estimated food consumption, blood pressure measurements, ECG, respiratory rate and depth, neurobehavior, clinical pathology including weekly albumin determination and urinalysis, as well as blood and tissue immunophenotyping (bone marrow, left axillary lymph node and spleen) were assessed. Complete necropsies were performed on all animals with recording of macroscopic abnormalities, organ weights, and microscopic examination. Blood was collected for intensive bioanalysis of rozanolixizumab, total IgG and ADA. The treatment was well tolerated, and only the expected pharmacological changes were found to be treatment related (Table 4).

In the 13-week repeated dose study, the study design encompassed treated groups as in the 4-week study, but also a SC group which received rozanolixizumab intermittently, every 3 days in weeks 1, 6 and 10 (e.g., 6 treatments in total). Investigations performed during this study were the same as those performed in the 4-week toxicology study (see above) with the addition of immune function assessment -the effect of rozanolixizumab on the primary and secondary T-dependent antibody response (TDAR) to keyhole limpet haemocyanin (KLH) – and the inclusion of measurements of serum cytokines and

complement activation markers (to further explore any immunostimulatory impact of ADAs). As expected, rozanolixizumab treatment resulted in decreased anti-KLH IgG titers in the TDAR assessment (but did not affect the IgM response) in animals dosed with 50 and 150 mg/kg SC every 3 days as well as in animals dosed with 150 mg/kg iv every 3 days. The effect was not as pronounced for animals dosed with 150 mg/kg SC every 3 days in Weeks 1, 6, and 10 only.

In the 26-week study, a minimal study design was chosen, with only a control group and one dosed group /150 mg/kg SC). Parameters evaluated in this study included mortality, clinical observations, body weight, body temperature, ophthalmic observations, clinical pathology (including haematology and clinical chemistry), urinalysis, blood analyses, immunological endpoints (TDAR, immunophenotyping, complement and cytokine analyses), and the terminal analyses of organ weights, tissue immunophenotyping in immune organs, and macroscopic and microscopic pathology. Male fertility endpoints were testicular and semen evaluation. Female fertility endpoints were menstrual cyclicity monitoring and ovarian/uterine maturation stage. No hormone analysis was performed. Blood was collected for intensive bioanalysis of rozanolixizumab, total IgG (measured by reversed phase UPLC coupled with MS/MS) and ADA.

Table 4: Toxicology studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
NDC2447 GLP	Cynomolgus Monkey Main study 3 M/F Recovery 2 M/F (control and high dose groups only)	0, 50 or 150 mg/kg sc 150 mg/kg iv Dosing every 3 days for 4 weeks	4 weeks Recovery minimum 8 weeks	NOAEL 150 mg/kg sc or iv	Pharmacological findings of decreased levels of IgG, albumin, globulin and total protein Inflammatory cell infiltrates at injection sites
NCD2448 GLP	Cynomolgus Monkey Main study 3 M/F (0 mg/kg) 4 M/F (treated groups) Recovery 2 M/F (control and 150 mg/kg dose groups only)	0, 50, 150 mg/kg sc 150 mg/kg iv Dosing every 3 days Except Group 4 (150 mg/kg sc) dosed twice weekly in week 1, 6 and 10	13 weeks Recovery 8 weeks	NOAEL 150 mg/kg sc or iv	All treated groups: minimal perivascular mononuclear cell infiltrates in brain (Table 5) Minimal to marked inflammation at injection sites
NCD2553 GLP	Cynomolgus monkey Main study 3 M/F (0 mg/kg) 6/8 * M/F (treated group) Recovery 2 M/F	0, 150 mg/kg sc every 3 days	26 weeks Recovery 8 weeks	Males: 150 mg/kg Females: not possible to establish NOAEL due to ADA related immune complex formation in one female (removed from study in week 9)	150 mg/kg: Pharmacological findings of decreased levels of IgG, albumin, globulin and total protein Minimal to marked inflammation at injection sites Two animals: Perivascular inflammatory cell infiltrates in 2 females; lung, kidney or in lung, liver, caecum and heart Accompanied by increased levels of C3a
NCD2617 Non-GLP	Rhesus Monkey 3 M	150 mg/kg iv	1 week	150 mg/kg	Pharmacological findings of decreased IgG and TP. Increased albumin/globulin ratio

* 1 female was excluded from the study in week 9, due to lack of PD effect, likely due to ADA, 2 females were included in the treated group to replace the animal taken down prematurely.

In the 13-week study, an increased incidence (compared to controls) of perivascular mononuclear cell infiltrates was observed the meninges of the brain in dosed animals. In the cerebral parenchyma (mainly affecting the cerebral cortex), perivascular cuffs (mononuclear cells infiltrating the adventitia of a part or the complete circumference of a brain vessel) were found to occur with higher incidence in dosed animals (Table 5).

Table 5: Incidence of infiltrate in the brain of terminally sacrificed animals, separated into infiltrate/meningeal and perivascular cuff (infiltrate in the parenchyma). Male and female animals combined.

Group	**1**	**2**	**3**	**4**	**5**
Treatment	**0mg/kg/day s.c. (every 3 days)**	**50mg/kg/day s.c. (every 3 days)**	**150mg/kg/day s.c. (every 3 days)**	**150mg/kg/day s.c. (3 times over 13 weeks)**	**150mg/kg/day i.v. (every 3 days)**
No. examined	**6**	**8**	**8**	**8**	**8**
Infiltrate/ Meningeal	1	7	4	6	6
Perivascular cuff	1	2	4	2	1

Both meningeal infiltrates and parenchymal perivascular cuffs were graded as 'minimal' and were not associated with any evidence of neuronal cell degeneration or glia cell response.

The repeat dose studies were primarily performed in cynomolgus monkey, as the NHP was found to be the only pharmacological relevant species. Following observations of diarrhoea, vomiting, headaches, and pyrexia in initial clinical studies the rhesus monkey was explored as possible a relevant animal model to establish if this animal model would be representative of the clinical observation. No signs of toxicity comparable to the AEs observed in the clinical studies were noted in the 3 male animals administered 150 mg/kg rozanolixizumab. No further *in vivo* studies were undertaken in other species.

In general, the nonclinical toxicity studies showed mainly expected pharmacological effects of decreased IgGs, TP and to a lesser extent decreased albumin. General nonspecific inflammatory cell infiltrations were observed across studies and study groups, but most were characterised as nonspecific incidental findings expected in cynomolgus monkeys of Asian origin. A few animals in all studies showed soft or liquid faeces on some occasions, but both animals in control groups, as well as in treated groups presented with this finding.

However, in the 13-week study, a higher incidence of perivascular mononuclear cell infiltrates in brain was observed in all treated groups compared to control animals. The applicant was asked to elaborate further on these findings and a comprehensive argumentation for not linking the findings of CNS perivascular infiltrates of mononuclear cells in monkeys to headache in patients was provided (see discussion). Furthermore, in the 26-week study, histologic brain observations include infiltration of inflammatory cells in choroid plexus noted in 2 females in the treated groups (vs 1 in control) and perivascular infiltration of inflammatory cells (in the brain) in 1 female in the treated and control group respectively. At recovery, singular findings were made in the treated female group. The incidences in the 26-week study, are more comparable with the literature incidences reported (Butt 2015, Chamanza 2010), and were dismissed by the study director (together with a variety of inflammatory cell infiltrations in various tissues) as incidental finding within expected background data for cynomolgus monkey.

In the 26-week study, one female was taken down in week 9 due to loss of PD and ADA response. Two new females were included in the study, resulting in a total of 8 females in the treated group. In general, the findings were mainly expected pharmacological effects, however 2 females did present with perivascular inflammatory cell infiltrates; lung, kidney or in lung, liver, caecum and heart, these findings were accompanied by increased levels of C3a in the two affected females. The findings were considered adverse in the lung of female 18660, hence only a no-observable-adverse-effect level (NOAEL) for males could be set, as only one dose level was used in this study.

2.5.4.3. Genotoxicity

Rozanolixizumab is a mAb of the IgG4 isotype comprising native non-modified amino acids and does not contain any chemical linkers or chelators. Rozanolixizumab acts by binding to FcRn on cells for which there is no evidence of a direct mutagenic effect. MAb are not considered to be genotoxic as they do not gain access to the cytoplasm or nucleus of cells and therefore do not directly interact with deoxyribonucleic acid (DNA), alter DNA integrity, or influence the cell cycle. For these reasons, and in accordance with the International Council for Harmonisation (ICH) Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1) (EMA/CHMP/ICH/731268/1998), genotoxicity studies were not performed.

2.5.4.4. Carcinogenicity

In line with ICH S6(R1) a carcinogenicity risk assessment has been provided, discussing the relevance and need for *in vivo* carcinogenicity studies.

Conventional carcinogenicity studies are not appropriate for rozanolixizumab because:

- The IgG4 chemical structure itself does not represent a carcinogenic risk.
- Rozanolixizumab is a human mAb, which is not pharmacologically active in rodents, and carcinogenicity studies are not feasible in the cynomolgus monkey.
- Based on the weight of evidence in the literature available to date in preclinical models, neutralizing FcRn does not suggest an increased tumour-promoting risk.
- Nonclinical models have proven unsuccessful in informing on cancer risks of immunomodulatory biologics and would not provide further useful information on top of what is already known.
- The highly specific mode of action of rozanolixizumab is to block FcRn (a non-signalling receptor) resulting in reduced serum IgG levels. Decreased serum IgG has not been associated with increased cancer risk in humans.
- Rozanolixizumab has not been shown to impact cellular immunity important in antitumor immune responses; 4-week, 13-week and 6-month repeat dose toxicity studies in Cynomolgus monkeys showed a lack of effects on cellular immune function or signs of as tissue hyperplasia or dysplasia, increased organ weight or cell proliferation, and, in keeping with a lack of observed cellular immunosuppression, there were no signs of lymphoproliferative changes, pre-cancerous or cancerous lesions.
- There is limited and conflicting literature evidence from experimental mouse models proposing a potential role for FcRn in antigen presentation to tumour-specific CD8+ T cells and in protective anti-tumour immunity.
- However, the overall weight of evidence from the literature suggests that rozanolixizumab would not be expected to have a neither a strong nor a direct impact on anti-oncogenic virus promotion and anti-tumour CD8+ T- and NK-cells responses.

2.5.4.5. Reproductive and developmental toxicity

No stand-alone fertility and early embryonic development studies have been conducted with rozanolixizumab. Given that only the NHP was found to be a relevant species – an ePPND study was performed in cynomolgus monkeys.

Fertility endpoints were assessed as part of the 26-week repeat dose study in sexually mature cynomolgus monkeys. Only a high dose group (150 mg/kg every 3 days) as well as control were included in this study to minimise the number of animals used. Menstrual cyclicity and testicular analysis were included in this study. No effect of rozanolixizumab was observed on male reproductive endpoints (ejaculate weight, sperm count, sperm motility, or morphology). The applicant concluded similarly for female reproductive endpoints (menstrual cyclicity or ovarian/uterine maturation status). However, the applicant was requested to discuss the findings as 3 females (of 8) did show irregular menstrual bleeding. Upon clarification, it could be agreed that the observed changes in menstrual cycling appeared to be linked with clinical or group dynamic reasons and not with a direct effect of rozanolixizumab on female fertility (see discussion). –No apparent effects on embryofoetal development were observed following SC administration with 50 or 150 mg/kg rozanolixizumab to pregnant cynomolgus monkeys every three days from GD 20.

No apparent effects on prenatal and postnatal development were observed following SC administration with 50 or 150 mg/kg rozanolixizumab to pregnant cynomolgus monkeys every three days from GD 20 until parturition. A slight trend towards an earlier parturition (mean duration of pregnancy of 157 Days in control group, 156 Days in 50 mg/kg and 152 days in 150 mg/kg groups) were observed. However, the duration of pregnancy in all groups were within the is within the historical reference values for gestation length (mean ± standard deviation 160.2±7.0 days; N=134), but it could not be excluded that the duration of gestation was affected by administration of rozanolixizumab.

Incidentally, infant mortality was higher in the control group compared to the treated groups, but the number of live infants on PND 8 and 180 were comparable across all groups (10 to 12 infants).

Expected pharmacological effects were observed in dams. Maternal animals that successfully gave birth and infants survived had active rozanolixizumab concentrations, low ADA response, expected PD in the maternal animals, and no transfer of maternal IgG to the infants. However, the generally small albumin decreases may have been due to steric hindrance by the bound mAb, which prevented albumin access to FcRn. The decreased levels of these 3 parameters normalised by LD 28. A decrease in IgG titers, with no effect on IgM titers, represented the expected pharmacology for rozanolixizumab, but no trend for enhanced IgG clearance was noted in infants of rozanolixizumab -treated maternal animals.

T-cell dependent antibody response in pups indicated that the IgG titer and IgM titer after primary immunisation on PND 119 and secondary immunisation on PND 147 were within the variability of the control group.

2.5.4.6. Toxicokinetic data

See above.

2.5.4.7. Local tolerance

Local tolerance endpoints were included in the repeat dose studies in cynomolgus monkeys. Local irritation in the form of minimal to marked inflammation was observed at the SC injection sites and increase in severity was observed with increased frequency of injections. The local inflammatory reactions subsided during the recovery period.

These findings correlate with adverse drug reactions (ADR) as described in section 4.8 (List of adverse reactions) of the SmPC, in which injection site reactions (injection site rash, reaction, erythema, inflammation, discomfort and infusion site pain) are categorised as common.

2.5.4.8. Other toxicity studies

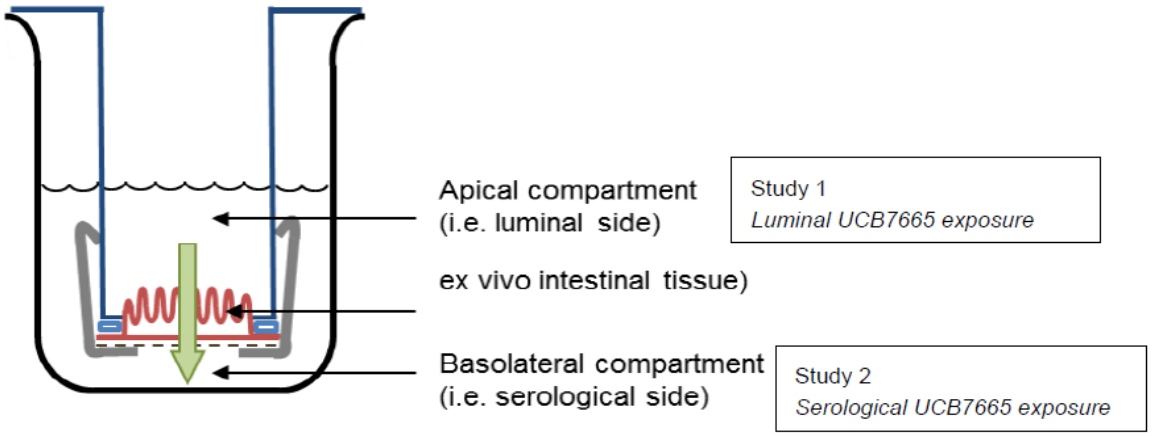
Development of ADA was observed in the repeat-dose toxicity studies, especially those of longer duration and more in female compared to male monkeys.

In vitro tissue cross reactivity (TCR) studies were performed in support of the species selection, as well as to further elucidate on comparability of human and cynomolgus monkey tissue binding similarity (or differences) following observations of AEs in the early clinical trials. In general, there was good concordance between the specific positive staining observed in the human and cynomolgus monkey in a standard panel tested. Specific positive staining was observed with fluorescein isothiocyanate conjugated rozanolixizumab in vascular endothelium, epithelial cells, urothelium, connective tissue, glomerular mesangeum and smooth muscle in both the human and cynomolgus monkey and additionally within the endoneurium and thecal/granulosa cells in the cynomolgus monkey. An additional TCR study, including GI and CNS tissues was performed to elucidate on the observed differences in AE observed in clinic and nonclinical studies. Notable inter-species differences were observed within the mucosal epithelial cells (more intense and consistent staining within human tissue) and myenteric ganglia (more overt positive staining within cynomolgus monkey tissue) of the GI tract, and microvascular endothelial cells (more continuous and intense staining within cynomolgus monkey tissue) of the CNS.

The ability of rozanolixizumab to induce cytokine release was examined in a comprehensive *in vitro* test regimen. Positive controls induced cytokine release as expected, whereas rozanolixizumab did not under the tested circumstances.

In addition, an *in vitro* study using human intestinal tissue (ileum and colon) in an using chamber was performed in order to inform on the potential effects of rozanolixizumab on human GI tissue including tissue viability, permeability and histology and to (ii) evaluate test item-mediated changes in the release of a panel of eicosanoid lipid mediators which includes: prostaglandins, prostaglandins metabolites and other mediators (e.g. leukotrienes), identified from literature as potential biomarkers of GI injury or homeostasis (from here on referred to as 'eicosanoid lipid mediators'). The test system was divided in two studies where rozanolixizumab concentrations of 10 µg/mL or 100 µg/mL was exposed either apically (Study 1) or basolaterally (Study 2) – see figure below. Rozanolixizumab did not induce any significant changes the tested biomarkers for GI injury in the current study under the circumstances tested.

Figure 2: Schematic representation of the InTESTine model indicating the apical and basolateral compartments



2.5.5. Ecotoxicity/environmental risk assessment

The active substance is a humanised monoclonal antibody, which is expected to be metabolised by proteolysis, and therefore, rozanolixizumab is not expected to pose a risk to the environment.

Similarly, the product composition does not contain any substances which are cause for concern with regards to environmental risk assessment.

2.5.6. Discussion on non-clinical aspects

Pharmacology and mechanism of action

Rozanolixizumab is designed to increase clearance of IgG to clear pathogenic autoantibodies in patients of autoimmune diseases by inhibiting the salvage mechanism of IgG at the FcRn. It is acknowledged that this may be a beneficial strategy.

Results from binding and affinity studies support the use of cynomolgus monkey as non-clinical testing species.

The mechanism of action is considered well-established for rozanolixizumab both *in vitro* and *in vivo* and supported by meaningful effects as observed in *in vivo* disease models (ITP and MOGAD), however not in a model of gMG. This can be accepted as the underlying cause or mechanism of disease is similar.

There seemed to be a large discrepancy in exposure between a human FcRn-transgenic (hFcRn Tg) mouse administered human IgG and humans at which relevant effect (decrease in plasma IgG) is obtained. Comparing effective plasma concentrations between an artificial system such as the transgenic mouse expressing the human FcRn receptor and patients is complex. Factors which increase the complexity of comparison are i) different levels of expression of target between mouse and human, ii) different routes of administration, iii) allometric scaling, iv) the inherent complexity of target mediated drug disposition of a protein obliterating its own rescue mechanism. The studies in the transgenic mouse model can be accepted as a non-clinical proof of concept for the mechanism of action of rozanolixizumab, which cannot be used for e.g. informing on effective doses or plasma concentrations in the patient as the effective FcRn expression is most likely less than in "normal" humans. However, comparison of exposure-response relationships between monkey and humans should be feasible.

From data obtained in the GLP-compliant 4- and 13-week repeat-dose toxicity studies, it can be concluded that rozanolixizumab show minimal potential for impact on cardiovascular, respiratory, or neurobehavioral parameters.

Pharmacokinetics

Rozanolixizumab is a humanised IgG4 mAb raised in rats and is therefore a victim of its own inhibition of the IgG salvage mechanism by FcRn. Hence, the half-life, is in the vicinity of 130 hours in humans (SmPC) and around 30 hours in monkeys as determined from Day 1 in the 4-weeks study (IV 150 mg/kg), much shorter than the normal 21-23 days in humans and 8 days in monkeys of IgGs. This makes PKPD modelling quite complex as the human PopPK model reflects. Moreover, it should be noted that the monkeys quite quickly developed ADA against rozanolixizumab increasing the variability of exposure and effect over time emerging 1-2 weeks after the first dose. However, exposure in general did not decrease to a degree of hampering the validity of the pivotal toxicity studies. All studies provided a comfortable safety margin to human exposure at the highest dose levels.

A wealth of PK studies providing an immense amount of data were conducted. Data included both PK (free and total rozanolixizumab), PD (total IgG) and ADA measures (both screening and titres). Total

rozanolixizumab was not determined in the ePPND study; this is acceptable as it is not a requirement in general to analyse for both free and total medicinal product.

All the methods appear robust and were validated to GLP. The ADA assay, which is semiquantitative (relative to control), was also validated to GLP and appeared fit for purpose. However, only the primary data was claimed GLP-compliant and not the secondary and exploratory calculation of cut-point and related assay sensitivity was not. ADA assays do not have to be GLP compliant, hence this is acceptable. The LC-MS/MS method for quantification of IgG as a PD biomarker appeared sufficiently qualified but was not claimed GLP compliant. This is acceptable as this analyte is a biomarker. The ratio of total and free rozanolixizumab changed from study to study were the free was higher than total in the 4-week study, similar in the 13-week study and lower in the 26-week study. This could be to be attributed to analytical method variability, but most importantly interindividual variability in the monkeys themselves. Moreover, the incidence and amounts of ADA (binding and/or neutralising) typically increase with time, gaining opportunity to impact exposure of free rozanolixizumab.

No distribution, metabolism or excretion studies were submitted. This Is acceptable for mAb and in line with ICH S6.

Primary and secondary PK parameters was presented for monkeys and humans. The values were derived from PKPD mixed-effects modelling which is acceptable. Moreover, an accepted publication on PK-PD modelling of the anti-FcRn mAb rozanolixizumab: Translation from preclinical stages to the clinic was submitted in support of the presented PK parameters (Lledo-Garcia et al, 2022). Finally, model derived human exposure was used to calculate margins of safety, when compared with non-compartmentally derived exposure of free rozanolixizumab in monkeys in the toxicology studies. Margin of safety is in the range of 36-228 and therefore fully acceptable.

Rozanolixizumab is inclined to increase clearance for other IgG based products and this is also reflected in the Summary of Product characteristics (SmPC) section 4.5. No non-clinical or clinical studies were submitted to characterise this effect. Since the mechanism is well-understood, this is acceptable from a non-clinical perspective. Whether PK monitoring of patients in concomitant treatments with rozanolixizumab and another IgG product is necessary will be a clinical matter.

The repeat-dose toxicity studies of 4-, 13- and 26-week duration provide the basis for the safety evaluation of the dosing regimen in patients. Monkeys were dosed either SC or IV at dose levels of 50 or 150 mg/kg every three days, where patients are dosed once weekly in cycles of 6 weeks.

ADA development is quite common in both monkeys and patients (up to 65%, 10% being neutralising), which for patients seem somewhat high considering rozanolixizumab is a humanised antibody, but of rat origin. This trait is inherent in many antibody drugs as they are typically initially raised in rodents and thereafter grafted and/or mutated for humanisation. It should be noted that ADAs against rozanolixizumab are generally not impacting the IgG lowering effect in both monkeys and patients, i.e., the pharmacological effect is retained.

As a potential cause for high incidence of ADAs in patients, it was suggested that as FcRn, apart from being responsible for IgG recycling, FcRn is also implicated in antigen presenting processes in concert with FcγRs in dendritic cells and further down the line promotes CD4+ priming and expansion. It could then be speculated that ADAs towards rozanolixizumab is initiated through its FcRn binding in dendritic cells in which it is presented to MHCs.

Moreover, studies show that FcRn expression within DCs enhances CD8+ T cell activation against cognate Ags and mediates e.g., mucosal immunity. This effect is marked not only by increased cross-presentation but also by increased secretion of IL-12, a potent CD8+ T cell activator. Moreover, enhanced IL-12 secretion upon stimulation with immune complexes is only possible when FcRn function is intact within the stimulated DCs (Qi & Cao, 2021).

This could indicate that the limited secondary immune response towards rozanolixizumab is dampened due to the general FcRn inhibition/target occupation.

In both the 13- and 26-week studies, female monkeys more often developed ADAs against rozanolixizumab leading to decrease of effect and free rozanolixizumab.

The ePPND study was well-designed and offered a wealth of PK data (free rozanolixizumab), ADA and IgG data in the mothers and sparse, but informative sampling in the infants for rozanolixizumab. While the mothers developed ADA against rozanolixizumab over time instigating high variability in exposure and response in the low dose group, the high dose group-maintained exposure through gestation and even showed some accumulation of rozanolixizumab towards the end of the study. Hence, the study is accepted to have fulfilled its purpose in terms of exposure. Further, the study was well-designed for characterising how rozanolixizumab interferes with IgG transfer between the mother and foetus by inhibiting FcRn in placenta. applicant concluded *that when ADAs appear in the mother during pregnancy, loss of exposure of rozanolixizumab occurs, leading to normal transfer of maternal IgG through the placenta to the fetus. This data also shows that rozanolixizumab significantly impedes maternal transfer of IgGs across the placenta in animals with active concentrations of rozanolixizumab.* This is endorsed.

Toxicology

Only NHP were used for the toxicology studies performed. This is supported, as Rozanolixizumab was shown to bind to both recombinant and cell-bound FcRn from human and cynomolgus monkey with equivalent affinities. No other relevant nonclinical species were identified.

Following observations of diarrhoea, vomiting, headaches, and pyrexia in initial clinical studies the rhesus monkey was explored as a possible relevant animal model to establish if this would be representative of the clinical observations. No signs of toxicity comparable to the AEs observed in the clinical studies were noted in the 3 male animals administered 150 mg/kg rozanolixizumab. No further *in vivo* studies were undertaken in other species. This is supported.

TK analysis revealed ADA formation following repeated administration in several animals. ADAs did not affect the validity of the repeat-dose studies and the toxicological conclusions could be drawn from the studies.

In general, the nonclinical toxicity studies showed mainly expected pharmacological effects of decreased IgGs, TP and to a lesser extent decreased albumin. General nonspecific inflammatory cell infiltrations were observed across studies and study groups. However, in the 13-week study, infiltration of inflammatory cells in the brain were observed in higher incidences than expected. Since headache is a very common adverse effect in patients, the applicant was asked to elaborate further on these findings. A comprehensive argumentation for not linking the findings of CNS perivascular infiltrates of mononuclear cells in the 13-week repeat-dose toxicity study in monkeys to headache in patients was provided. The argumentation is accepted, since:

i. The incidence of the finding was similar despite difference in posology (continuous vs intermittent) and was still present despite loss of PD effect.

ii. Absence of dose-response effect.

iii. At the end of the recovery phase, the incidence of meningeal infiltrates was increased in control animals compared to rozanolixizumab-treated animals.

iv. The finding was minimal and not considered adverse and was not observed in the 4-week or the 26-week study.

v. Similar findings were observed in a 4-week study of an antibody targeting an extracellular target. By the end of the 13-week treatment-free period in this study, the distribution, incidence and

severity of these infiltrates were similar between control and previously treated animals and comparable to the incidence and severity at the end of treatment period.

vi. These CNS findings are also observed as a spontaneous background finding in cynomolgus monkeys (Chamanza et al, 2010; Sato et al, 2012, Butt et al, 2015).

Similar findings were noted in the 26-week study, however as this study had incidences similar to historical data, and only one treated group – no relation to treatment could be established. In addition, two females presented with perivascular inflammatory cell infiltrates; lung, kidney or in lung, liver, caecum and heart, these findings were accompanied by increased levels of C3a. The lung finding in female 18660 was considered adverse, and likely to be caused by immune complex formation and deposition and proinflammatory stimulation related to complement activation.

Headache is linked to increased levels of IgG in the brain. A literature review revealed conflicting data on the role of FcRn at the level of the blood brain barrier. FcRn may not be responsible for translocating excess IgG out of the brain across the blood brain barrier. Instead, it is believed that levels of IgG in the brain follows the levels in the periphery. Hence, rozanolixizumab should lower levels of IgG in brain and the cause for the high incidence of headache during treatment with rozanolixizumab is still unknown.

Rozanolixizumab is a mAb that are not considered to be genotoxic. In accordance with the International Council for Harmonisation (ICH) Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1) (EMA/CHMP/ICH/731268/1998), genotoxicity studies were not performed. This is endorsed.

The applicant did not provide carcinogenicity studies which is supported. The provided carcinogenicity assessment supports the lack of any conventional carcinogenicity studies. The company proposed to monitor potential AEs of malignancies through pharmacovigilance activities, this is supported.

Given that only the nonhuman primates (NHP) was found to be a relevant species – an ePPND study was performed in cynomolgus monkeys. No stand-alone fertility and early embryonic development studies have been conducted with rozanolixizumab. Fertility endpoints were included in the pivotal 26 weeks repeat dose study. The lack of a standalone fertility and early embryonic development is in line with current guidance. No treatment related effects were observed with respect to male fertility parameters. The same was concluded regarding the female parameters but in the view of the changes in menstrual cycling in 3 females this was not initially accepted. Upon request, the applicant clarified that these findings were linked to diarrhoea and/or weight loss in 2 of the animals, and changes in the hierarchy due to one female being removed from the cage in treatment week 9– hence the relation to treatment is not clear. It should however also be noted that only 1 treated group was included in the 26-week study, hence the number of animals exposed was limited, and any dose relationship would not be possible to ascertain. However, it is agreed that, as the observed changes in menstrual cycling appear to be linked with clinical or group dynamic reasons, any direct effect of rozanolixizumab on female fertility is not expected. In the ePPND study, no test item-related macroscopic or microscopic changes were observed in any stillborn, unscheduled sacrifice (moribund), infants found dead or in maternal animals and infants at the terminal sacrifice.

Local tolerance endpoints were included in the repeat dose studies in cynomolgus monkeys. Local irritation was observed at the SC injection sites and increase in severity was observed with increased frequency of injections. These findings correlate with ADR as described in section 4.8 (List of adverse reactions) of the SmPC.

In vitro tissue cross reactivity (TCR) studies, there was good concordance between the specific positive staining observed in the human and cynomolgus monkey in a standard panel tested. An additional TCR study, including GI and CNS tissues performed to elucidate on the observed differences in AE observed in clinic and nonclinical studies found notable inter-species differences. The applicant claimed that these

quantitative differences are unlikely accountable for toxicological inter-species differences observed between healthy cynomolgus monkey and healthy human. This is supported.

The ability of rozanolixizumab to induce cytokine release was examined in a comprehensive *in vitro* test regimen. Rozanolixizumab did not under the tested circumstances.

To explain the GI AEs observed in initial clinical trials, an *in vitro* study was undertaken in human GI tissue. The test system was originally developed (by TNO) to study GI permeability of compounds in a more physiological setting. Rozanolixizumab did not induce any significant changes in the tested biomarkers for GI injury in the current study under the circumstances tested. It was comparable to a reference IgG4 not expected to induce any changes. A positive control mAb capable of inducing GI injury under the test system circumstances were not included to show that the system was fit for purpose.

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

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary PD studies provided adequate evidence of MoA, which is considered well-established for rozanolixizumab both *in vitro* and *in vivo* and supported by meaningful effects as observed in *in vivo* disease models, however not in a model of gMG.

From the PK point of view, the non-human primate was the most relevant species for non-clinical efficacy and safety studies. Then non-clinical PK data are considered acceptable.

Overall, the toxicology programme revealed expected findings of pharmacologic effects in the form of decreased IgG, TP and to a lesser extent, decreased albumin.

The MA application can be considered approvable from a nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study no./ region (countries)	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ dosage regimen/ route of administration	Duration of treatment	No. of study participants for each treatment/ M/F[a]	Mean age of study participants/ range[a]	Study status/ type of report
5.3 Clinical Study Reports								
5.3.3 Reports of Human PK Studies								
5.3.3.1 Healthy Participant PK and Initial Tolerability Study Reports								
UP0018/ UK	Safety, PK, and PD	Phase 1, participant-blind, investigator-blind, randomized, placebo-controlled	Healthy study participants	Rozanolixizumab or placebo/ ascending doses of 1mg/kg, 4mg/kg, and 7mg/kg/ iv and sc	Single dose	49 participants randomized to 6 cohorts with a ratio of 3:1 (N=6 rozanolixizumab and N=2 placebo)/ M=42/F=7	44 years/ 22 to 65 years	Complete/ Final CSR
UP0060/ UK	Safety, tolerability, PK, and PD	Phase 1, participant-blind, investigator-blind, randomized, placebo-controlled	Healthy study participants	Rozanolixizumab or placebo/ Cohort 1: 4mg/kg Cohort 2: 7mg/kg Cohort 3: 10mg/kg/ sc	Single dose	65 participants from 3 ethnicities: 22 Japanese (N=16 rozanolixizumab; N=6 placebo), 20 Chinese (N=16 rozanolixizumab; N=4 placebo), and 23 Caucasian (N=17 rozanolixizumab; N=6 placebo)/ M=30/F=35	Japanese participants: 34.1 years/ 22 to 59 years Chinese participants: 34.1 years/ 20 to 49 years Caucasian participants: 40.9 years/ 20 to 60 years	Complete/ Final CSR
UP0106/ UK	Safety, tolerability, PK, and PD	Phase 1, participant-blind, investigator-blind, randomized, placebo-controlled	Healthy study participants	Rozanolixizumab or placebo/ 280mg and 560mg/ sc	Single dose	Approximately 32 participants (planned)/ TBC[a]	≥18 years[a]	Clinically complete/ Study reporting is ongoing
5.3.5 Reports of Efficacy and Safety Studies								
5.3.5.1 Study reports of controlled clinical studies pertinent to gMG								
Studies with a placebo control								
MG0002/ Canada, Europe, and US	Efficacy, safety, tolerability, PK, and PD	Phase 2a, multicenter, randomized, investigator- and participant-blind, placebo-controlled, 2-arm, repeat dose, treatment sequence	Study participants with gMG	Rozanolixizumab or placebo/ 3x7mg/kg or placebo (1-week intervals) 3x7mg/kg or 3x4mg/kg (1-week intervals)/ sc	Dosing Period 1: 4 weeks Dosing Period 2: 2 weeks	43 participants Dosing Period 1: Placebo (N=22) 7mg/kg (N=21) Dosing Period 2: Placebo-7mg/kg group (N=11) Placebo-4mg/kg group (N=11) 7mg/kg-7mg/kg group (N=10) 7mg/kg-4mg/kg group (N=10)/ M=16/F=27	51.9 years/ 25 to 81 years	Complete/ Final CSR
MG0003/ Asia, Canada, Europe, and US	Efficacy and safety	Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm, repeat dose	Study participants with gMG	Rozanolixizumab or placebo/weight-tiered doses of 6x7mg/kg or 6x10mg/kg or 6xplacebo (1-week intervals)/ sc	6 weeks	200 participants Rozanolixizumab 7mg/kg (N=66) Rozanolixizumab 10mg/kg (N=67) Placebo (N=67) M=79/F=121	51.8 years/ 18 to 89 years	Complete/ Final CSR
5.3.5.2 Study reports of uncontrolled clinical studies								
MG0004/ Asia, Canada, Europe, and US	Safety, tolerability, and efficacy	Phase 3, multicenter, randomized, OLE to MG0003	Study participants with gMG	Rozanolixizumab weight-tiered doses of 7mg/kg or 10mg/kg QW/ sc	52 weeks	71 participants Rozanolixizumab 7mg/kg (N=35) Rozanolixizumab 10mg/kg (N=36) M=33/F=38	52.2 years/ 19 to 89 years	Complete/ Final CSR
MG0007/ Asia, Canada, Europe, and US	Safety, tolerability, and efficacy	Phase 3, multicenter, OLE to MG0003 and MG0004	Study participants with gMG	Rozanolixizumab at weight-tiered doses of 7mg/kg or 10mg/kg QWx6/ sc	6 weeks prn[b]	165 participants Rozanolixizumab 7mg/kg (N=88) Rozanolixizumab 10mg/kg (N=77) M=69/F=96	52.7 years/ 18 to 89 years	Ongoing/ Interim CSR

2.6.2. Clinical pharmacology

The clinical pharmacology programme includes PK, PD, and immunogenicity data from 8 completed and ongoing clinical studies. These include 3 Phase 1 studies: FIH study in healthy participants (UP0018), a safety, tolerability, PK, and PD study of rozanolixizumab in Japanese, Chinese, and Caucasian healthy participants (UP0060), and a safety, tolerability, PK, and PD study of rozanolixizumab administered via manual push versus syringe driver to healthy participants (see table above). PK data from study UP0106 was not initially presented although some data has been used for PK/PD modelling. The study report was presented during the procedure.

An additional 5 Phase 2 and Phase 3 studies provide supportive data including PK, PD, and immunogenicity of rozanolixizumab. These studies include a Phase 2a study in participants with gMG (MG0002), a Phase 2 study in participants with either primary persistent or chronic ITP (TP0001), and 3 Phase 3 studies in participants with gMG (1 double-blind, placebo-controlled study [MG0003] and 2 open-label extensions [MG0004 and MG0007]; MG0007 is still ongoing) (see table above).

The dosing of rozanolixizumab in MG0003, MG0004, and MG0007 was based on a weight tiered approach with different fixed doses across 4 body weight tiers (Table 6).

Table 6: Rozanolixizumab doses by weight tiers in MG0003, MG0004 and MG0007

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

SC=subcutaneous

An exploratory PopPK-PD model was developed on observed PK and total IgG data from 1 Phase 2 study and 2 Phase 1 studies. The purpose of the model was to support dose selection for the Phase 3 studies.

A second PopPK-PD model was developed on observed PK and total IgG data from 3 Phase 1 studies, 2 Phase 2 studies, and 2 Phase 3 studies, as well as MG-ADL score data from MG0003. The models were extended with disease-specific autoantibody data from 1 Phase 2 study and 2 Phase 3 studies in gMG.

2.6.2.1. Pharmacokinetics

Population PK analyses

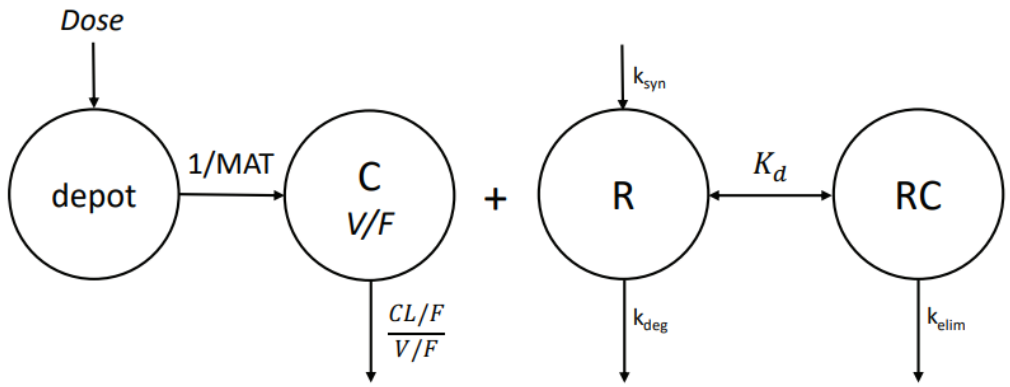
The popPKPD analyses were performed with a nonlinear mixed effects modelling approach using NONMEM with first-order conditional estimation with interaction. Dose regimen simulations, data management and further data processing were performed using various R packages.

PopPKPD models for rozanolixizumab was developed with data from healthy volunteers, patients with MG, and patients with ITP using plasma concentrations of rozanolixizumab and total serum IgG concentrations from 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. Model

development was based on 898 rozanolixizumab plasma concentrations (2058 rozanolixizumab plasma concentrations excluded) from 266 participants (65 healthy volunteers, 154 MG patients, and 47 ITP patients), 5566 total IgG levels from 412 participants (103 healthy volunteers, 243 MG patients, and 66 ITP patients), 1202 anti-AChR observations from 203 MG patients, 116 anti-MuSK observations from 17 MG patients, and 2180 MG-ADL scores from 200 MG patients.

The final popPKPD model consisted of three sub-models, describing the longitudinal plasma rozanolixizumab concentrations, serum total IgG, and anti-AChR concentration, respectively. The PK sub-model was a one compartment disposition model with a first-order absorption, with a first-order elimination from the central compartment, in addition to a TMDD model implemented using the quasi-equilibrium assumption (Figure 3).

Figure 3: Schematic illustration of rozanolixizumab PK model



C: Plasma concentration of rozanolixizumab; R: free concentration of receptor; RC: drug receptor complex; FcRn: independent t CL/F; FcRN independent apparent clearance; V/F apparent volume of distribution, Kd: dissociation constant; Ksyn: receptor synthesis rate constant; Kdeg: receptor degradation rate constant; Kelim: complex elimination rate constant; MAT: mean absorption time.

The total IgG and anti-AChR sub-models were indirect response models with fraction of FcRn bound to rozanolixizumab increasing the antibody clearances. Separate baseline parameter, maximum effect (E_{max}), and degradation half-life were estimated for total IgG and anti-AChR. The drug effect on increasing antibody clearances was described as a function of the degree of saturation of FcRn after binding to rozanolixizumab. Body weight effect on FcRn independent apparent clearance (CL/F), apparent volume of distribution (V/F) and total IgG baseline (power relations); lyophilised formulation effect on mean absorption time (MAT); effect of steroid use at baseline on both total IgG baseline and rozanolixizumab E_{max} on total IgG reduction; ITP population effect on V/F; and time varying ADA/neutralizing antibodies (Nab) effect on FcRn independent CL/F were the covariate-parameter relationships included in the final PK-tIgG-AChR model. Inter-individual variability (IIV) was associated with nine parameters: FcRn independent CL/F, V/F, MAT, total IgG baseline, total IgG half-life, total IgG E_{max}, anti-AChR baseline, anti-AChR E_{max}, and proportional residual unexplained variability (RUV) for anti-AChR. Combined proportional and additive RUV model was specified for rozanolixizumab and anti-AChR and a proportional model was used for total IgG. A fourth sub-model was developed to characterise the relationships between rozanolixizumab exposure and anti-MuSK, but anti-MuSK related parameters were estimated with high uncertainty and not deemed fit for the purpose of simulating the time course of anti-MuSK and MG-ADL in the evaluation of a 2-fixed dose regimen in comparison to weight tiered dosing regimens.

Parameter estimates of the final population model for rozanolixizumab and selected diagnostic plots are shown in Table 7 and Figures 4 to 7.

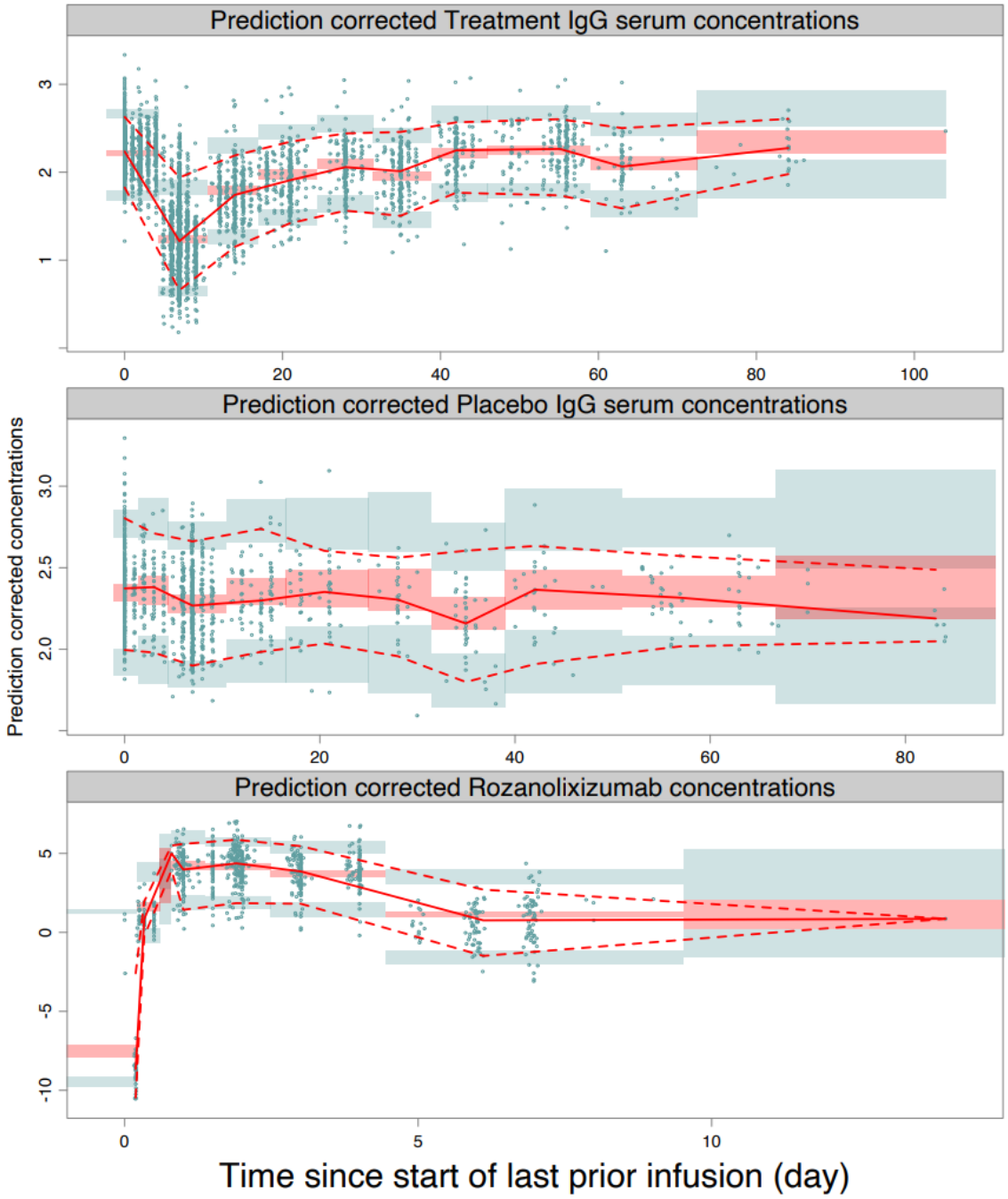
Table 7: Parameter estimates of the final PK-tIgG-AChR model.

	Final PK-tIgG-AChR model*
Run	106
OFV	14371.61
Condition number	98.43

		Final PK-tIgG-AChR model*		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
F1		1.00		
MAT	day	1.85	6.74	
FcRn independent CL/F	L/day	0.879	12.8	
V/F	L	6.41	4.90	
$FcRn_{tot}$	nmol/L	165	5.24	
K_{deg}	day^{-1}	0.548	4.36	
K_d	nmol/L	2.09	9.35	
Total IgG baseline	g/L	10.7	1.74	
Total IgG half-life	day	18.7	4.09	
Total IgG E_{max}		3.33	4.45	
Anti-AChR baseline	nmol/L	4.82	17.2	
Anti-AChR half-life	day	11.4	7.73	
Anti-AChR E_{max}		2.51	11.8	
Formulation on MAT		-0.445	16.7	
Weight on FcRn independent CL/F		1.35	20.8	
Weight on V/F		0.808	8.41	
Weight on total IgG baseline		-0.150	33.6	
ADA +ve/ NAb -ve on FcRn independent CL/F		-0.319	23.2	
ADA +ve/ NAb +ve on FcRn independent CL/F		1.76	23.5	
Steroids on total IgG baseline		-0.170	12.7	
Steroids on total IgG E_{max}		0.229	28.3	
ITP on V/F		0.466	13.5	
IIV MAT	(CV)	0.490	7.37	30.8
IIV FcRn independent CL/F	(CV)	0.535	20.0	63.6
IIV V/F	(CV)	0.245	5.81	22.6
IIV total IgG baseline	(CV)	0.234	4.01	2.31
IIV total IgG half-life	(CV)	0.437	4.09	12.1
IIV total IgG E_{max}	(CV)	0.379	5.50	13.9
IIV anti-AChR baseline	(CV)	1.87	6.16	0.440
IIV anti-AChR E_{max}	(CV)	1.12	6.70	14.7
IIV RUV anti-AChR prop.	(CV)	0.231	13.2	31.8
RUV PK prop.	(CV)	0.370	3.32	10.2
RUV PK add.	nmol/L	1.91	3.52	10.2
RUV total IgG prop.	(CV)	0.113	0.298	10.2
RUV anti-AChR prop.	(CV)	0.274	3.69	10.2
RUV anti-AChR add.	nmol/L	0.0257	10.2	10.2

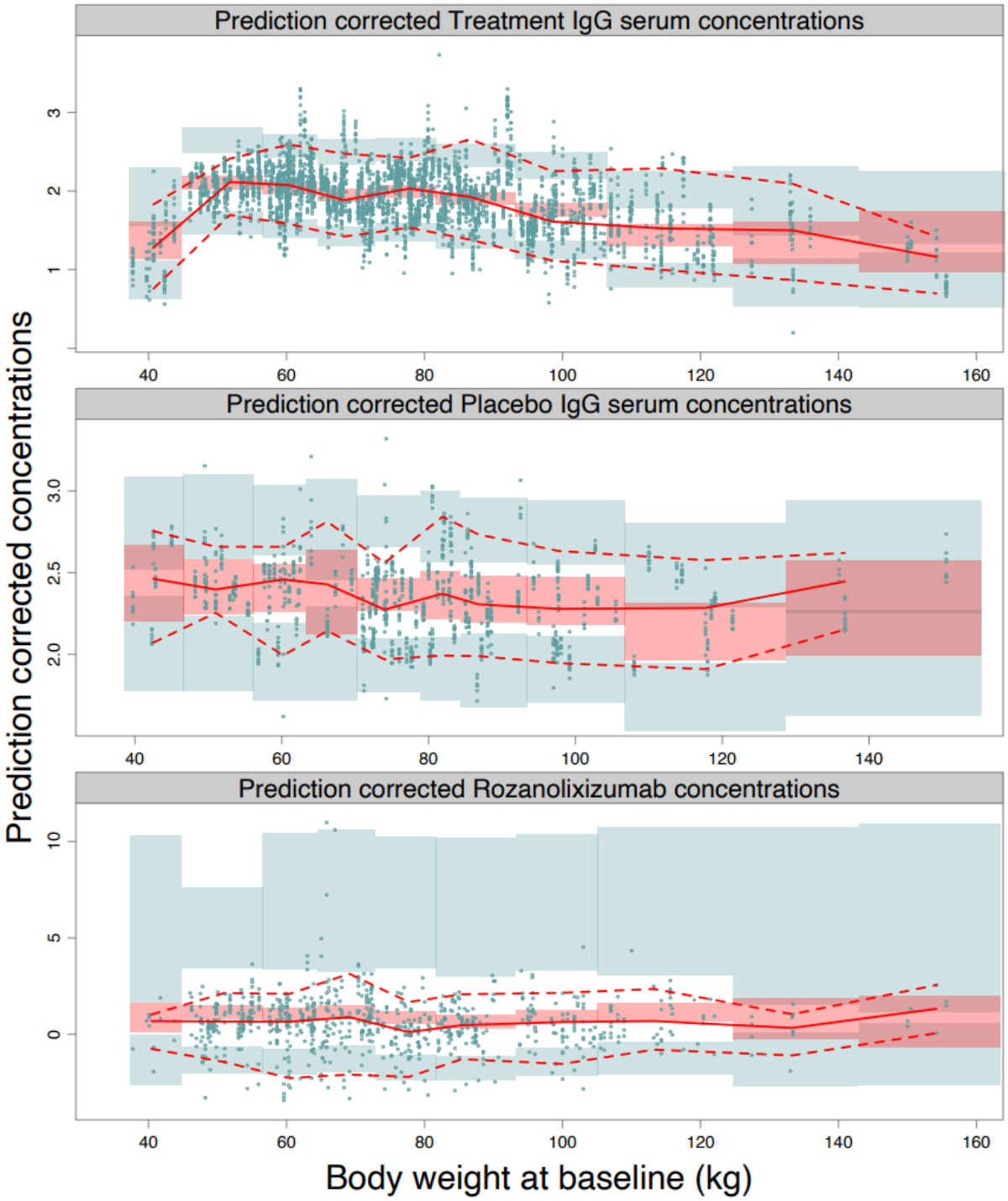
The final PK-tIgG-AChR model is also the base PK-tIgG-AChR model.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.
Formulation effect on MAT if of the lyophilised formulation relative to the liquid formulation.

Figure 4: Prediction-corrected visual predictive check (pc-VPC) 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 based PK-IgG model.



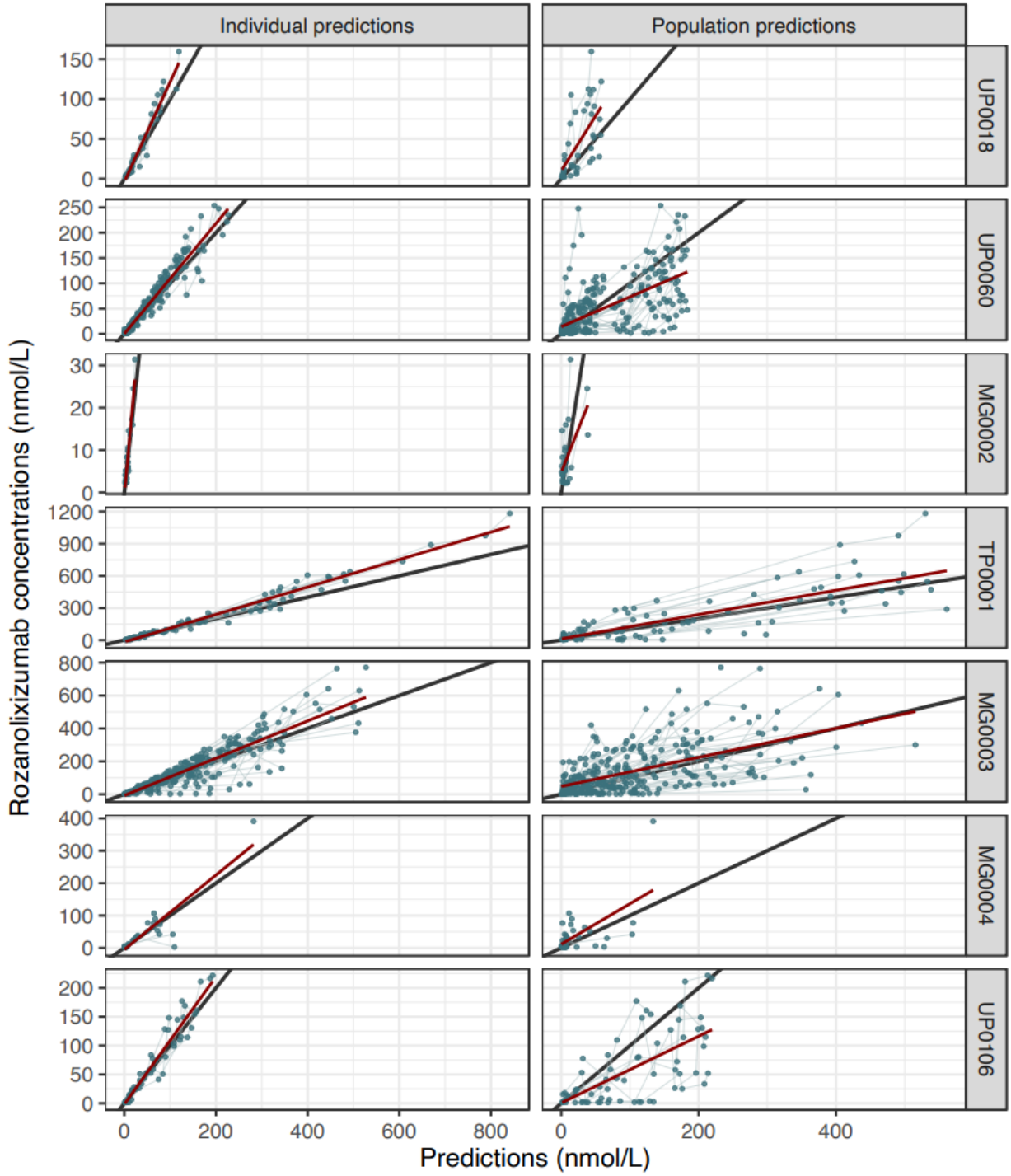
Individual prediction corrected observations are indicated by green dots. The solid and dashed red lines represent the median, 5th and 95th percentiles of the prediction corrected observations; the shaded pink and green areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.

Figure 5: Prediction-corrected visual predictive check (pc-VPC) of log-transformed rozanolixizumab and IgG concentrations versus body weight stratified by groups: placebo and treatment, based on 500 simulated data sets, using the based PK-IgG model.



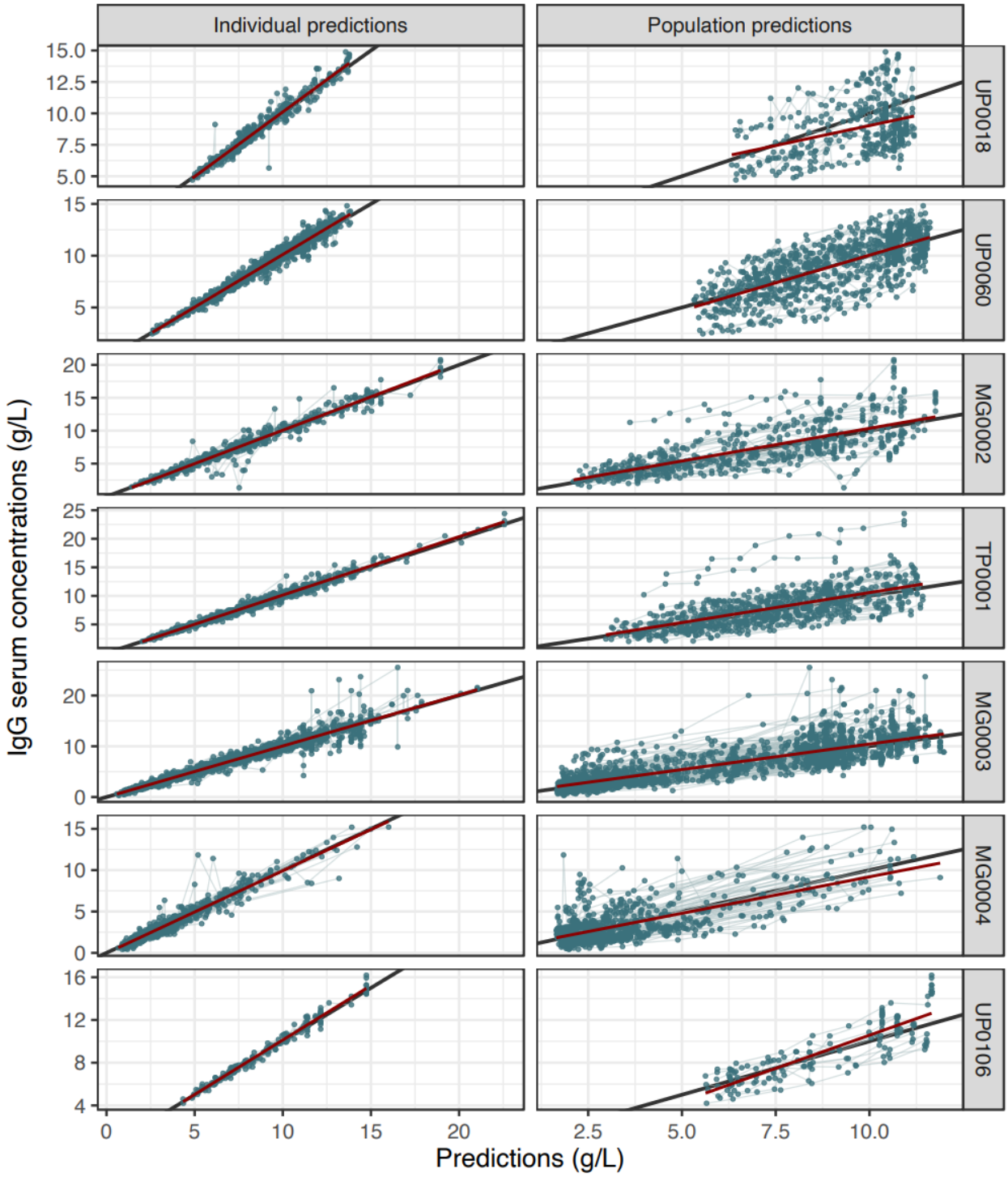
Individual prediction corrected observations are indicated by green dots. The solid and dashed red lines represent the median, 5th and 95th percentiles of the prediction corrected observations; the shaded pink and green areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.

Figure 6: Observed rozanolixizumab concentrations versus population and individual predictions from the final PK-IgG model on a linear scale, stratified by study.



Individual data points are indicated by dots and the points for each individual are connected with a line. The diagonal black line is the line of identity, and the solid red line is a smooth.

Figure 7: Observed IgG serum concentrations versus population and individual predictions from the final PK-IgG model on a linear scale, stratified by study.



Individual data points are indicated by dots and the points for each individual are connected with a line. The diagonal black line is the line of identity, and the solid red line is a smooth.

Exposure-efficacy models (tIgG-MG-ADL, AChR-MGADL and MuSK-MG-ADL)

The final tIgG-MG-ADL model was a direct response model with a placebo effect. The effect of rozanolixizumab was assumed to be exerted through the decline in total IgG, expressed as relative change from baseline in percent. Interindividual variability was supported on MG-ADL score Baseline, the placebo response, and the maximum effect on MG-ADL at a complete reduction of total IgG ($E_{max,MGADL}$). MGFA disease class at baseline was included as a predictor of the baseline MG-ADL score.

No other statistically significant covariates (age, sex, region, stratification factor [MuSK positive and AChR positive], baseline steroid usage, duration of disease, thymectomy at Baseline) were found to influence MG-ADL score/total IgG correlation.

Parameter estimates of the final model are presented in the Table 8. The final tIgG-MG-ADL model was externally evaluated using MG0002 data.

Table 8: Parameter estimates of the final PKPD 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	
$E_{max,MG}$		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 $E_{max,MG}$	(CV)	3.23	10.4	33.9
IIV Placebo	(CV)	1.30	11.6	27.1
RUV		1.65	0.844	8.18

The RSE for IIV and RUV parameters are reported on the approximate SD scale.
$E_{max,MGADL}$ is the maximum effect on MG-ADL at an IgG change from baseline of -100% constrained between 0 and 1, and γ is the effect of MGFA disease class at baseline on baseline MG-ADL.

The final model for anti-AChR effects on MG-ADL was a direct response model with the time-dependent placebo effects and the anti-AChR effects reducing the MG-ADL score. The relationship between percent change from baseline anti-AChR concentration and relative change from Baseline MG-ADL score was described by a power function. Interindividual variability was supported on MG-ADL Baseline, placebo response, and $E_{max,MGADL}$. $E_{max,MGADL}$ increased with increasing baseline anti-AChR concentration. This effect was, however, small in relation to the IIV in $E_{max,MGADL}$. No other statistically significant covariates (age, sex, region, Baseline steroid usage, duration of disease, thymectomy at Baseline) were found to influence $E_{max,MGADL}$. The final model parameter estimates are presented in Table 9.

Table 9: Parameter estimates of the final AChR-MG-ADL model.

	Final AChR-MG-ADL model
Run	8
OFV	4471.37
Condition number	7.92

		Final AChR-MG-ADL model		
	Unit	Value	RSE (%)	SHR (%)
MG-ADL baseline	score	8.11	4.34	
$E_{max,MG}$		0.256	24.9	
Placebo	/day	0.000974	18.6	
Shape parameter for $AChR_{PCFB}$ and $E_{max_{MG-ADL}}$ relationship		0.460	4.48	
MGFA disease class on MG-ADL baseline		0.143	44.2	
Baseline anti-AChR on $E_{max_{MG-ADL}}$		0.0941	27.1	
IIV MG-ADL baseline	(CV)	0.384	6.80	9.16
IIV $E_{max,MG}$	(CV)	2.53	11.9	29.7
IIV Placebo	(CV)	1.41	14.9	27.6
RUV		1.69	0.934	8.33

The RSE for IIV and RUV parameters are reported on the approximate SD scale.
$E_{max,MG}$ is the maximum effect at an anti-AChR change from baseline of -100%, constrained between 0 and 1. The effect of MGFA disease class at baseline on baseline MG-ADL is governed by γ (equation 16). The shape parameter for predicted percent change from baseline anti-AChR on $E_{maxMG-ADL}$ is determined by ØachR, baseline (equation 20)
Formulation effect on MAT if of the lyophilised formulation relative to the liquid formulation.

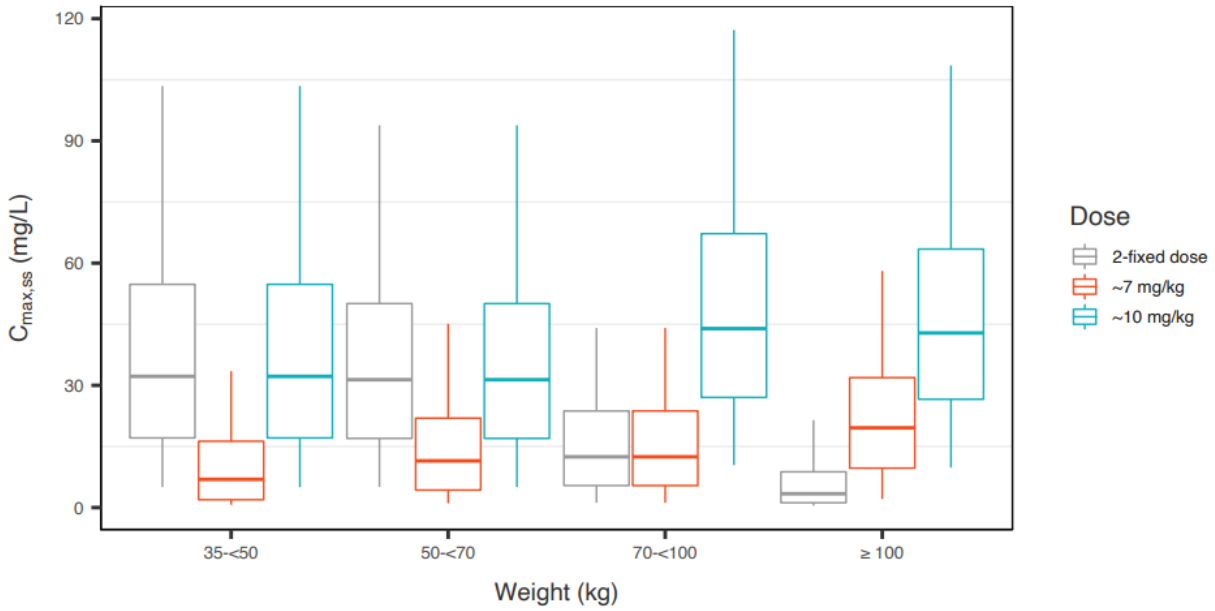
The final model for anti-MuSK effects on MG-ADL was a direct response model with rozanolixizumab effects being subtractive on the Baseline of MG-ADL modelled on the logit scale. Interindividual variability was supported on MG-ADL baseline and $E_{max,MGADL}$. In the analysis of anti-MuSK effects on MG-ADL, no placebo effects could be described, and no covariate effects were tested due to limited data and large variability.

Simulations to assess a 2-fixed dose regimen

Simulations were conducted using the PK-tIgG, PK-tIgG-AChR, tIgG-MG-ADL and AChR-MG-ADL models to predict rozanolixizumab exposures, reduction in total IgG and anti-AChR autoantibodies, and changes from MG-ADL baseline resulting from 2-fixed dosing and to compare with those for the Phase 3 weight-tiered dosing regimen. Anti-MuSK autoantibody levels were not simulated due to the high uncertainty associated with the anti-MuSK related parameters in the PK-PD analysis.

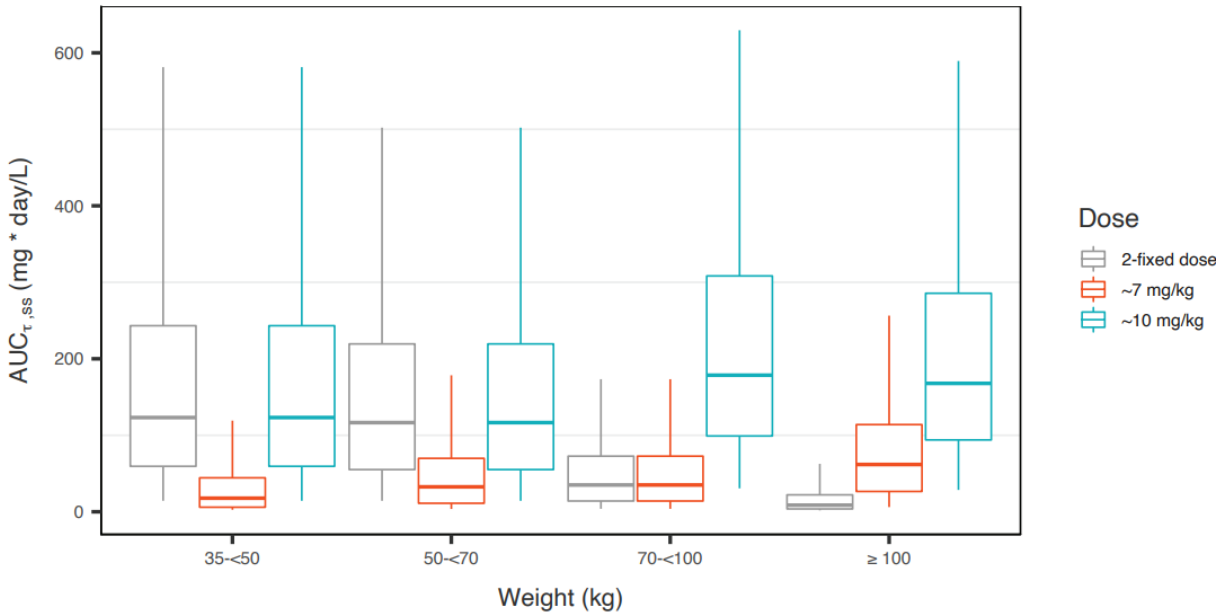
Simulated distributions of rozanolixizumab maximum concentration during a dosing interval at steady state ($C_{max,ss}$) and area under the concentration-time curve during a dosing interval at steady state ($AUC_{tau,ss}$), in the MG population following six weekly SC administrations of the 2-fixed dose regimen, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight categories are presented in Figure 8.

Figure 8: Box Plot of the $C_{max,ss}$ in the MG population following 6 weekly SC administration of the 2-fixed dose, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight.



The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and 75th percentiles, whiskers extend between 5th and 95th Percentiles.

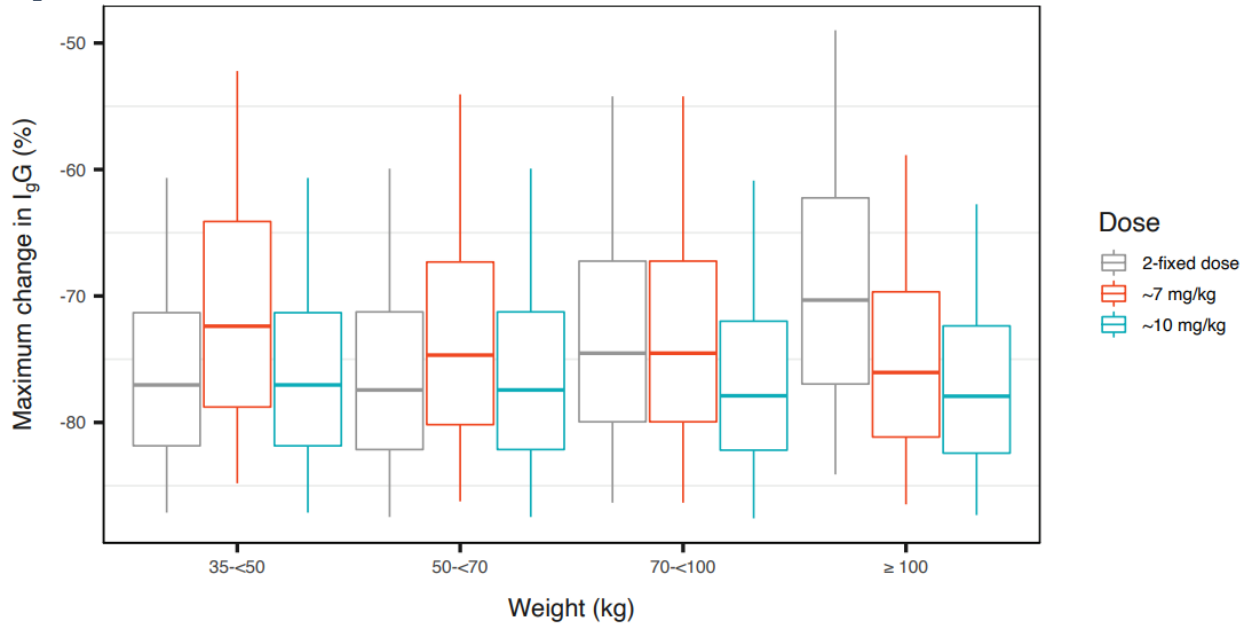
Figure 9: Box Plot of the $AUC_{tau,ss}$ in the MG population following 6 weekly SC administration of the 2-fixed dose, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight.



The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and 75th percentiles, whiskers extend between 5th and 95th Percentiles.

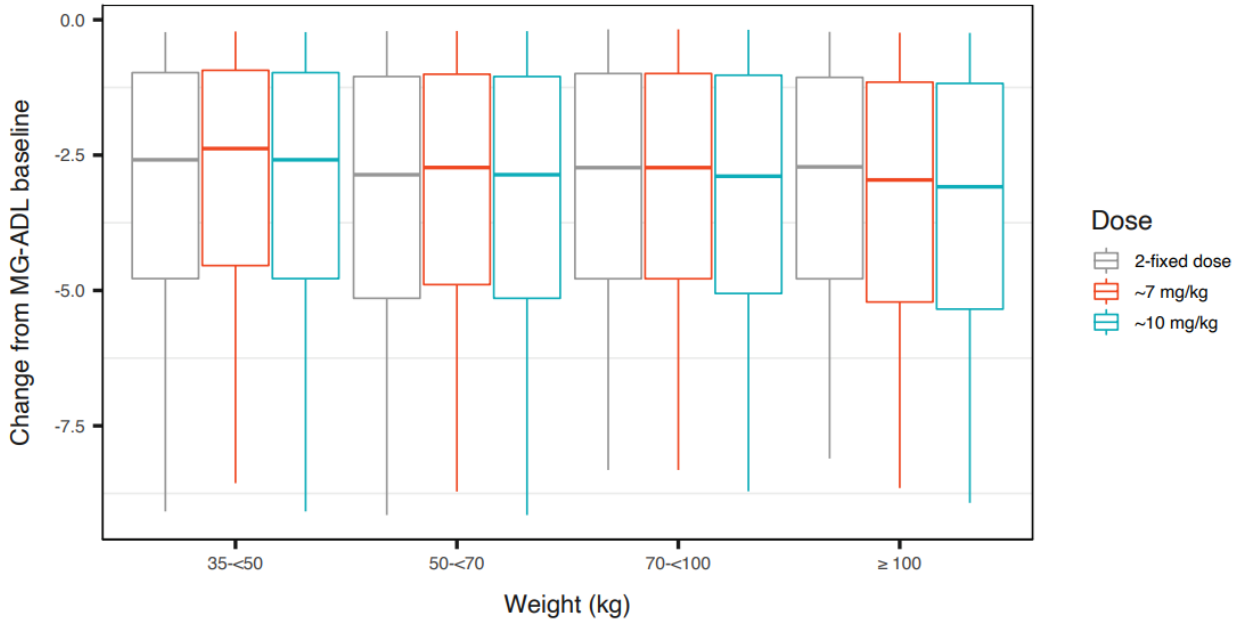
Simulated boxplots of rozanolixizumab maximum change from baseline IgG and change from MG-ADL score baseline on day 43 in the MG population following six weekly S.C. administrations of the 2-fixed dose regimen, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight categories are presented in Figures 10 - 11.

Figure 10: Box Plot of the maximum percent change from baseline IgG in the MG population following 6 weekly SC administration of the 2-fixed dose, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight.



The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and 75th percentiles, whiskers extend between 5th and 95th Percentiles.

Figure 11: Box Plot of the change from MG-ADL score baseline on Day43 in the MG population following 6 weekly SC administration of the 2-fixed dose, weight tiered ~7mg/kg and ~10mg/kg dosing versus weight.



The horizontal line in the middle of the boxes is the median, the boxes indicate the 25th and 75th percentiles, whiskers extend between 5th and 95th Percentiles.

The simulated distribution of $C_{max,ss}$ and change from MG-ADL score baseline in the weight group population are summarised (mean, median, 5th and 95th percentiles) for each dosing regimen in the weight group population in Tables 10 – 12..

Table 10: The simulated $C_{max,ss}$ in the weight group population for selecting dosing.

Dose		$C_{max,ss}$ (mg/L)			
	Weight (kg)	Mean	Median	5th percentile	95th percentile
2-fixed dose					
	35	63.44	54.66	14.37	146.39
	42	43.89	36.62	7.75	111.89
	49	27.66	23.84	2.82	71.77
	50	62.46	54.69	13.17	133.88
	60	35.23	31.21	4.81	82.38
	69	27.98	22.88	2.10	68.24
	70	26.37	22.09	2.67	64.16
	85	15.15	12.28	1.13	41.28
	99	9.90	6.63	0.70	29.88
	100	10.04	7.06	0.68	26.75
	120	5.50	2.97	0.53	18.23
	140	3.09	1.32	0.40	13.08

~ 7 mg/kg					
	35	18.47	13.44	1.45	48.61
	42	12.15	8.06	0.91	36.98
	49	6.92	3.83	0.54	24.41
	50	28.29	23.49	2.61	70.33
	60	14.64	11.46	1.05	39.58
	69	11.20	7.34	0.63	32.96
	70	26.37	22.09	2.67	64.16
	85	15.15	12.28	1.13	41.28
	99	9.90	6.63	0.70	29.88
	100	34.00	30.29	4.72	78.91
	120	21.08	18.38	2.65	49.91
	140	13.23	10.33	1.43	36.79
~ 10 mg/kg					
	35	63.44	54.66	14.37	146.39
	42	43.89	36.62	7.75	111.89
	49	27.66	23.84	2.82	71.77
	50	62.46	54.69	13.17	133.88
	60	35.23	31.21	4.81	82.38
	69	27.98	22.88	2.10	68.24
	70	75.29	64.55	21.70	165.75
	85	48.12	41.40	10.28	105.26
	99	33.29	28.66	4.92	76.47
	100	68.23	59.62	19.14	141.02
	120	44.99	39.25	11.82	96.25
	140	30.04	26.33	7.22	72.68

Table 11: The simulated change from MG-ADL score baseline on Day43 in the weight group population for selected dosing.

Dose		**Change from MG-ADL score baseline**			
	Weight (kg)	Mean	Median	5th percentile	95th percentile
2-fixed dose					
	35	–3.69	–3.26	–9.04	–0.28
	42	–3.65	–3.23	–8.77	–0.24
	49	–3.84	–3.12	–9.54	–0.22
	50	–3.91	–3.32	–10.18	–0.23
	60	–3.63	–2.90	–10.25	–0.27
	69	–3.70	–3.01	–9.44	–0.35
	70	–3.55	–2.96	–8.69	–0.22
	85	–3.75	–3.40	–9.05	–0.28
	99	–3.59	–2.96	–9.41	–0.27
	100	–3.40	–2.94	–8.60	–0.25
	120	–3.40	–2.86	–8.78	–0.22
	140	–3.26	–2.84	–8.04	–0.24

~ 7 mg/kg					
	35	−3.49	−3.11	−8.62	−0.27
	42	−3.44	−3.02	−8.19	−0.24
	49	−3.56	−2.85	−9.10	−0.20
	50	−3.80	−3.29	−9.83	−0.23
	60	−3.48	−2.74	−9.94	−0.25
	69	−3.54	−2.79	−9.15	−0.34
	70	−3.55	−2.96	−8.69	−0.22
	85	−3.75	−3.40	−9.05	−0.28
	99	−3.59	−2.96	−9.41	−0.27
	100	−3.61	−3.12	−9.32	−0.26
	120	−3.67	−3.10	−9.32	−0.22
	140	−3.56	−3.14	−8.63	−0.25
~ 10 mg/kg					
	35	−3.69	−3.26	−9.04	−0.28
	42	−3.65	−3.23	−8.77	−0.24
	49	−3.84	−3.12	−9.54	−0.22
	50	−3.91	−3.32	−10.18	−0.23
	60	−3.63	−2.90	−10.25	−0.27
	69	−3.70	−3.01	−9.44	−0.35
	70	−3.67	−3.11	−8.88	−0.22
	85	−3.95	−3.55	−9.25	−0.28
	99	−3.82	−3.16	−9.66	−0.28
	100	−3.68	−3.22	−9.53	−0.27
	120	−3.79	−3.31	−9.49	−0.22
	140	−3.71	−3.23	−9.16	−0.26

Absorption

In the clinical programme, rozanolixizumab was administered by SC infusion in the right or left lower abdomen using a syringe pump. In healthy participants, maximum plasma concentrations of rozanolixizumab were achieved approximately 2 days after SC infusion (range of median values: 1.5 to 3 days). The PopPK estimate of the absolute bioavailability was 67%.

Table 12: Summary of rozanolixizumab pharmacokinetics in healthy participants and participants with generalised myasthenia gravis and immune thrombocytopenia

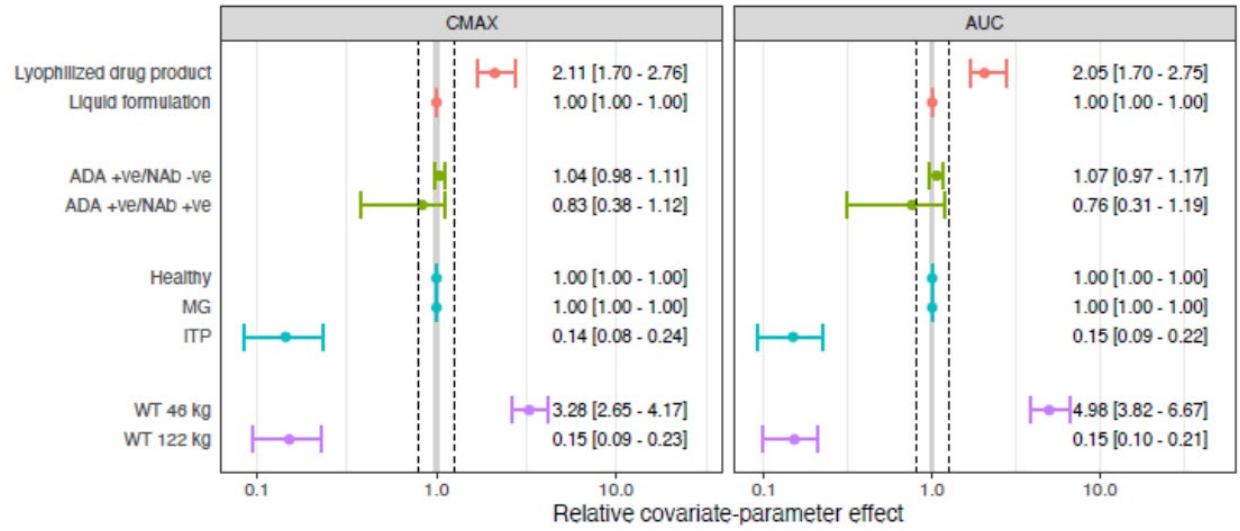
Study identifier	Study title	RLZ treatment	N	Parameter		
Healthy participants						
UP0018	A Subject-blind, Investigator-blind, Randomized, Placebo-controlled, First-in-Human Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Single Ascending Intravenous and Subcutaneous Doses of UCB7665 in Healthy Subjects			C_{max} (µg/mL)	$AUC_{(0-t)}$ (h.µg/mL)	t_{max} (h)
		Single dose (PK-PPS)		**GeoMean (GeoCV%)**	**GeoMean (GeoCV%)**	**Median (min, max)**
		1mg/kg iv	6	11.11 (17.0)	55.21 (54.8)	1.02 (0.98, 1.03)
		4mg/kg iv	6	89.33 (16.7)	2213 (21.3)	2.52 (1.02, 4.12)
		7mg/kg iv	6	154.5 (19.7)	5753 (20.5)	1.01 (1.00, 6.03)
		1mg/kg sc	6	NC	NC	NC
		4mg/kg sc	6	NC	NC	NC
		7mg/kg sc	6	12.41 (72.2)	643.3 (75.6)	48.15 (36.0, 71.9)
UP0060	A Randomized, Participant-blind, Investigator-blind, Placebo-controlled Study Comparing Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Subcutaneous Doses of Rozanolixizumab in Japanese, Chinese and Caucasian Healthy Volunteer Study Participants			C_{max} (µg/mL)	$AUC_{(0-t)}$ (day.µg/mL)	t_{max} (day)
		Single dose (PK-PPS)		**GeoMean (min, max)**	**GeoMean (min, max)**	**Median (min, max)**
		Caucasian 4mg/kg sc	4	2.428 (1.08, 4.27)	2.890 (0.826, 7.35)	1.500 (1.50, 2.00)
		Caucasian 7mg/kg sc	6	9.405 (2.57, 15.9)	21.62 (4.19, 50.8)	2.004 (1.50, 3.00)
		Caucasian 10mg/kg sc	6	19.74 (9.62, 37.5)	52.37 (16.4, 128)	3.000 (1.50, 3.00)
		Japanese 4mg/kg sc	4	0.5669 (0, 1.03)	0.4111 (0, 0.821)	NC (1.50, 1.50) [a]
		Japanese 7mg/kg sc	6	7.077 (1.67, 9.81)	16.79 (5.48, 23.9)	1.502 (1.50, 3.00)
		Japanese 10mg/kg sc	6	13.88 (1.63, 25.2)	44.78 (4.88, 86.5)	3.000 (1.50, 4.00)
		Chinese 7mg/kg sc	8	5.164 (0.444, 36.6)	10.80 (1.04, 86.4)	2.001 (1.50, 4.00)
		Chinese 10mg/kg sc	8	13.09 (4.16, 21.3)	39.64 (6.89, 72.2)	3.000 (2.00, 4.00)
Participants with generalized myasthenia gravis						
MG0003	A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients with Generalized Myasthenia Gravis			**Observed plasma concentrations (µg/mL)**		
				GeoMean (GeoCV%) [N]		
		Repeated dose Q1W (PK-PPS Set)		**Day 3**	**Day 24**	**Day 38 [b]**
		≈7mg/kg	64	3.8882 (775.4) [58]	6.8059 (478.1) [52]	5.3167 (3906.1) [4]
		≈10mg/kg	69	10.6200 (524.4) [62]	14.6544 (724.6) [62]	17.9867 (203.1) [5]
MG0007	An Open-label Extension Study to Evaluate Rozanolixizumab in Study Participants with Generalized Myasthenia Gravis			**Observed plasma concentrations (µg/mL)**		
				GeoMean (GeoCV%) [N]		
		Repeated dose Q1W (SS)		**Cycle 1 Day 3**		
		≈7mg/kg	79	2.3446 (932.9) [39]		
		≈10mg/kg	78	4.7888 (1366.7) [49]		
Participants with immune thrombocytopenia						
TP0001	A Multicenter, Open-label, Multiple-dose Study to Evaluate the Safety, Tolerability, and Efficacy of UCB7665 in Subjects with Primary Immune Thrombocytopenia			**Observed peak concentration (ug/mL) [c]**		
		Repeated dose Q1W (PK-PPS)		**GeoMean (GeoCV%)**	**Median (min, max)**	
		5x4mg/kg	4	NC	NC (BLQ, 8.36)	
		3x7mg/kg	8	NC	NC (BLQ, 25.1)	
		2x10mg/kg	10	12.80 (288.2)	24.55 (0.74, 54.4)	
		Single dose (PK-PPS)				
		1x15mg/kg	11	29.06 (107.2)	25.29 (7.49, 94.5)	
		1x20mg/kg	12	68.97 (43.4)	67.75 (40.1, 175)	

BLQ=below the limit of quantification; CSR=clinical study report; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; iv=intravenous; max=maximum; min=minimum; N=number of participants; NC=not calculated; PK=pharmacokinetic; PK-PPS=Pharmacokinetic Per-Protocol Set; Q1W=once weekly; RLZ=rozanolixizumab; SC=subcutaneous; SS=Safety Set
a n=2.
b PK substudy sampling.
c Peak concentration was defined as observed concentration 3 days after the final dose within a treatment group

Two different formulations were used during clinical development: the liquid formulation and the lyophilised formulation, with the liquid formulation being the proposed commercial formulation. No formal bioequivalence or bioavailability study has been conducted. The lyophilised formulation was used

in Phase 2 studies MG0002 and TP0001, In MG0002 all plasma concentrations were below the limit of quantification due to the sampling schedule used, therefore quantifiable PK data for the lyophilised formation are only available for ITP patients. In population PK-PD analysis CL0534, the lyophilised formulation was tested as a covariate on MAT and was found to have a shorter MAT than the liquid formulation, leading to a predicted 111% and 105% higher rozanolixizumab steady state C_{max} and AUC, respectively, after 6 weekly doses of 560mg (Figure 12). Immune thrombocytopenia patients were estimated to have an 86% lower $C_{max,ss}$ and 85% lower AUCss compared to healthy participants and gMG patients.

Figure 12: Forest plot showing the magnitude of covariate effects after a 560mg dose of rozanolixizumab on C_{max} and AUC.



+ve=positive; -ve=negative; ADA=anti-drug antibodies; CI=confidence interval; ITP=immune thrombocytopenia; MG=myasthenia gravis; Nab=neutralizing antibodies; WT=weight Note:
The reference patient is a 76kg 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 non-parametric bootstrap of 500 samples. The vertical gray line is marking no change, and the vertical dashed lines are marking the 0.8-1.25 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.

Food-interaction studies have not been provided as Rystiggo is administered subcutaneously.

Distribution

For a typical 76kg study participant (median body weight in the dataset), the estimated linear FcRn independent V/F was 6.6L (Table 13). The model development for CL0534 was based on data from SC administration only. The dataset did not include IV PK data and therefore the estimation of V is not possible based on the CL0534 analysis. However, the estimates for V from an exploratory PK-PD analysis are in good concordance with the estimate of 6.6 L for V/F (for a typical gMG patient of 76 kg) from the final popPK-PD model CL0534, considering an estimated F of 67%.

Table 13: CL0534 final population PK-IgG parameter estimates

Parameter	Unit	Value	RSE%	SHR (%)
FcRn independent CL/F	L/day	0.888	12.5	-
V/F	L	6.64	4.90	-
MAT	day	1.84	6.59	-
IgG Baseline	g/L	10.7	1.72	-
$FcRn_{tot}$	nM	163	5.06	-
K_d	nM	2.07	9.12	-
K_{deg}	day^{-1}	0.550	4.34	-
IgG half-life	day	18.8	4.01	-
E_{max}	-	3.24	4.49	-
PK Prop. RUV	(CV)	0.368	3.12	-
PK Add. RUV	nmol/L	1.91	3.53	-
PD Prop. RUV	(CV)	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	-
Formulation on MAT	-	-0.448	16.4	-
ADA positive/NAb negative effect on FcRn independent CL/F	-	-0.322	23.8	-
ADA positive/NAb positive effect 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	-
ITP on V/F	-	0.455	13.7	-
IIV CL/F	(CV)	0.546	19.3	63.1
IIV V/F	(CV)	0.247	5.79	23.5
IIV MAT	(CV)	0.485	7.37	31.8
IIV IgG Baseline	(CV)	0.233	3.96	2.13
IIV IgG half-life	(CV)	0.441	4.03	12.0
IIV E_{max}	(CV)	0.387	5.53	15.5

ADA=antidrug antibodies; Add=additive; CL/F=apparent clearance; CV=coefficient of variation; Emax=maximum effect; F=bioavailability; FcRntot=estimated total neonatal Fc receptor; IgG=immunoglobulin G; IIV=interindividual variability; ITP=immune thrombocytopenia; Kd=dissociation constant; Kdeg=receptor degradation rate constant; MAT=mean absorption time; Nab=neutralizing antibodies; PD=pharmacodynamic; PK=pharmacokinetic; Prop.=proportional; RSE=relative standard error; RUV=residual unexplained variability; SHR=shrinkage; V/F=apparent volume of distribution
Note: The RSE for IIV and RUV parameters are reported on the approximate standard deviation scale.

Elimination

Rozanolixizumab exhibits a PK profile compatible with TMDD with 2 elimination pathways: 1) a linear clearance pathway which is FcRn independent and represents typical proteolysis common to all immunoglobulins and 2) a nonlinear elimination pathway driven by binding of rozanolixizumab to FcRn, the receptor/target.

The rapid binding of rozanolixizumab to FcRn results in an estimated 81% to 91% of clearance of rozanolixizumab through FcRn binding at clinically relevant doses of ≈10mg/kg and ≈7mg/kg, respectively, with FcRn independent linear clearance representing a minor pathway.

The population estimate for the FcRn independent CL/F was 0.89L/day for a typical gMG patient of 76kg. The model development for CL0534 was based on data from SC administration only. The dataset did not include intravenous PK data and therefore the estimation of CL is not possible based on the CL0534 analysis. An estimate of CL was obtained in the exploratory population PK-PD analysis CL0460. In this analysis, CL was estimated to be 1.1L/day, which would equate to a CL/F value of 1.65L/day considering an estimated F of 67%. According to the applicant, the potential explanations for the apparent differences in estimates for CL and CL/F from the CL0460 and CL0534 models are the differences in structure and parametrisation of the models. In addition, the exploratory model did not include PK data obtained in the target gMG population.

It was not possible to calculate half-life for unbound rozanolixizumab in plasma due to the nonlinear PK profile of rozanolixizumab at therapeutic doses where rozanolixizumab plasma concentrations are undetectable within one week after dosing.

Rozanolixizumab is a humanised IgG4 full length antibody and is expected to be catabolised by degradation to small peptides and 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 cytochrome P450 metabolism or transporter-mediated disposition. Rozanolixizumab is not expected either to undergo renal excretion. As rozanolixizumab is not subject to hepatic metabolism, genetic polymorphism is therefore not expected to affect the elimination of rozanolixizumab.

Dose proportionality and time dependencies

Rozanolixizumab exposure increased in a greater than dose-proportional manner over a dose ranging from 1mg/kg to 20mg/kg following SC administration.

Through its binding to FcRn and formation of the complex, rozanolixizumab inhibits the FcRn IgG salvage pathway. As a result, the half-life of rozanolixizumab is reduced through increased catabolism to the extent that plasma levels at C_{trough} (1 week after dosing) are close to or BLQ in most patients, showing limited drug accumulation with weekly administration. Plasma concentrations were highly variable within and across treatment groups, particularly following SC administrations. See description of individual studies above.

Estimates of PK IIV (%CV) ranged from 24.7%-54.6% which is considered moderate.

Special populations

The effects of the statistically significant covariates on rozanolixizumab exposure at steady state are summarised in the forest plots in Table 12.

Impaired renal function

A dedicated renal impairment study has not been conducted. In the PopPKPD analysis, which included participants with mild and moderate renal impairment, estimated glomerular filtration rate (eGFR) (range: 38.2 to 161ml/min/1.73m2) did not show any significant impact on rozanolixizumab CL/F. The number of study participants and observations in the PK-IgG analysis data set are presented by renal impairment group in Table 14. The participants in the PK-immunoglobulin G (IgG) analysis dataset were classified as having no renal Impairment (eGFR ≥90ml/min/1.73m2), mild renal impairment (eGFR 60 to 89ml/min/1.73m2), or moderate renal impairment (30 to 59ml/min/1.73m2) based on their eGFR value at baseline (time=0).

Summary statistics of apparent clearance at time=0, and model predicted $C_{max,ss}$ and $AUC_{tau,ss}$ after weight-tiered dosing of ≈7mg/kg rozanolixizumab, stratified by renal impairment group at baseline, are presented in Tables 14 – 16.

Table 14: Participants with PK and IgG observations and number of observations presented by renal impairment group (PK-IgG)

Type Renal impairment	Number of participants	Number of observations	Number of observations/ Number of participants
Quantifiable rozanolixizumab concentration			
None	198	708	3.58
Mild	54	146	2.70
Moderate	14	44	3.14
All	266	898	3.38
IgG concentration			
None	296	3970	13.40
Mild	97	1366	14.10
Moderate	19	230	12.10
All	412	5566	13.50
All			
All	412	6464	15.70

eGFR= estimated glomerular filtration rate; IgG=immunoglobulin G; PK=pharmacokinetic.
Note: Renal impairment is defined as baseline eGFR ≥ 90ml/min/1.73m^2 (None); baseline eGFR 60-89ml/min/1.73m^2 (mild); baseline eGFR 30-59ml/min/1.73m^2 (moderate).

Table 15: Summary statistics of apparent clearance at time=0 in the final PK-IgG model, stratified by renal impairment group.

Apparent clearance (L/day)	None N=296	Mild N=97	Moderate N=19	Overall N=412
Mean (SD)	0.876 (0.339)	1.03 (0.420)	1.03 (0.343)	0.919 (0.366)
Median (min, max)	0.823 (0.127, 2.16)	0.981 (0.275, 2.52)	0.962 (0.307, 1.61)	0.859 (0.127, 2.52)

eGFR = estimated glomerular infiltration rate; IgG=immunoglobulin G; max=maximum; min=minimum PK=pharmacokinetic, SD=Standard deviation.
Note: Renal impairment is defined as baseline eGFR ≥ 90ml/min/1.73m^2 (None); baseline eGFR 60-89ml/min/1.73m^2 (mild); baseline eGFR 30-59ml/min/1.73m^2 (moderate).

Table 16: Predicted $C_{max,ss}$ and $AUC_{tau,ss}$ after 6 weekly weight-tiered doses of ≈7mg/kg rozanolixizumab based on individually predicted parameters, stratified by renal impairment group (PK-IgG)

		$C_{max,ss}$ (mg/L)				$AUC_{tau,ss}$ (mg*day/L)			
Renal impairment	N	Mean	Median	5th percentile	95th percentile	Mean	Median	5th percentile	95th percentile
None	296	15.0	12.7	1.24	38.5	45.8	34.6	3.69	125
Mild	97	17.6	16.8	2.26	36.6	54.9	40.6	5.27	152
Moderate	19	15.5	12.4	1.10	43.0	53.1	27.1	3.09	180

≈approximate dose; $AUC_{tau,ss}$ area under the concentration-time curve during a dosing interval at steady state, $C_{max,ss}$ maximum concentration during a dosing interval at steady state. eGFR = estimated glomerular infiltration rate; IgG=immunoglobulin G PK=pharmacokinetic,
Note: Renal impairment is defined as baseline eGFR ≥ 90ml/min/1.73m^2 (None); baseline eGFR 60-89ml/min/1.73m^2 (mild); baseline eGFR 30-59ml/min/1.73m^2 (moderate).

Impaired hepatic function

A dedicated hepatic impairment study has not been conducted. No data is available to allow identification and classification of hepatically impaired patients based on the Child-Pugh criteria.

Gender

Gender as co-variate had no impact on the PK of rozanolixizumab.

Race

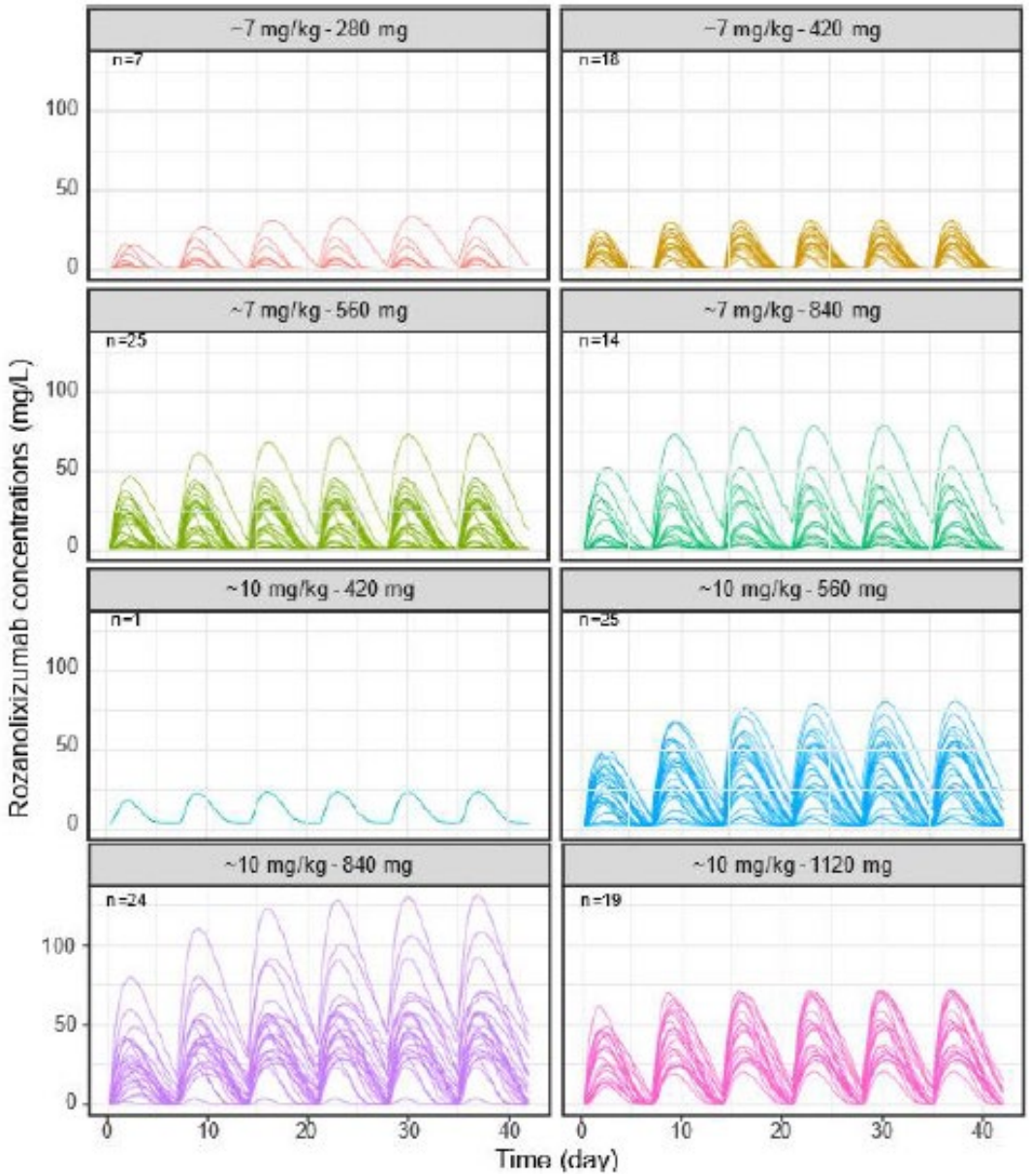
Ethnicity was not found to be a covariate on PK or PD model parameters, after accounting for the body weight.

Weight

Body weight was predicted to have the largest impact on rozanolixizumab exposure with an 85% lower $C_{max,ss}$ and 85% lower AUC_{ss} in a patient with the 97.5th percentile of the Baseline covariate value (122kg) and a 228% higher $C_{max,ss}$ and 398% higher AUC_{ss} in a patient with the 2.5th percentile of the baseline covariate value (46kg) relative to the reference patient of 76kg.

The rozanolixizumab PK profiles for study participants in the MG0003 study were predicted using the empirical Bayes estimates from the final PK-IgG model. For participants who had more than 1 dose level, only the highest dose level was used. The predicted rozanolixizumab PK profiles are presented by dose in Figure 13. Summary statistics of baseline continuous and categorical covariates are presented in the below tables. There appears to be greater variation in plasma concentration levels for the 840 mg dose, ~7 mg/kg and ~10 mg/kg dosing regimen as compared to the 1120 mg, ~10 mg/kg dosing regimen.

Figure 13: MG0003 predicted individual rozanolixizumab plasma concentrations vs. time stratified by dose and body weight tier (PK-IgG)



≈; approximate dose; EBE: empirical Bayes estimate; IgG: immunoglobulin G; PK: pharmacokinetic.
Note The number of study participants in each panel is shown in the left top corner. The predictions are based on the EBEs obtained from the final PK-IgG model. For participants who had more than 1 dose level, only the first dose is shown. Participants with dose levels that were not planned in the study protocol are not shown.

Table 17: MG0003: Baseline continuous covariate statistics for participants in the ≈7mg/kg dose group, stratified by dose level (PK-IgG)

Characteristic Statistic	≈7mg/kg 280mg N=7	≈7mg/kg 420mg N=18	≈7mg/kg 560mg N=25	≈7mg/kg 840mg N=14	Overall N=64
Age (years)					
Mean (SD)	58.6 (17.2)	45.3 (13.2)	53.6 (14.1)	60.1 (11.5)	53.2 (14.5)
Median (min, max)	59.0 (40.0, 89.0)	44.5 (22.0, 72.0)	52.0 (31.0, 83.0)	61.5 (38.0, 76.0)	52.0 (22.0, 89.0)
Body weight (kg)					
Mean (SD)	42.5 (3.45)	60.1 (4.49)	84.7 (8.62)	113 (21.5)	79.3 (25.4)
Median (min, max)	41.7 (37.7, 47.5)	60.0 (51.1, 68.0)	84.0 (70.5, 99.0)	107 (71.2, 154)	78.0 (37.7, 154)
Height (cm)					
Mean (SD)	155 (4.67)	162 (7.27)	172 (6.91)	179 (6.23)	169 (10.1)
Median (min, max)	154 (149, 163)	164 (149, 174)	171 (160, 188)	178 (170, 193)	170 (149, 193)
Body mass index (kg/m²)					
Mean (SD)	17.8 (2.14)	22.8 (2.12)	28.6 (3.46)	35.4 (6.76)	27.3 (6.83)
Median (min, max)	17.7 (14.2, 20.7)	22.6 (19.5, 27.0)	28.1 (23.8, 35.3)	33.6 (23.7, 47.6)	26.4 (14.2, 47.6)
eGFR (mL/min/1.73²)					
Mean (SD)	95.2 (21.9)	103 (14.1)	93.6 (17.9)	93.1 (17.2)	96.4 (17.3)
Median (min, max)	102 (57.1, 114)	100 (76.9, 136)	96.4 (56.9, 116)	92.6 (48.5, 113)	99.0 (48.5, 136)
ALT (U/L)					
Mean (SD)	14.7 (3.86)	17.4 (9.52)	21.4 (17.3)	28.1 (14.2)	21.0 (14.2)
Median (min, max)	13.0 (10.0, 20.0)	17.5 (7.00, 46.0)	17.0 (8.00, 91.0)	21.0 (13.0, 60.0)	18.0 (7.00, 91.0)
AST (U/L)					
Mean (SD)	20.6 (10.4)	17.8 (5.27)	23.3 (22.7)	22.3 (8.51)	21.2 (15.3)
Median (min, max)	18.0 (12.0, 43.0)	17.5 (10.0, 28.0)	18.0 (10.0, 127)	20.0 (13.0, 41.0)	18.0 (10.0, 127)
ALP (U/L)					
Mean (SD)	43.6 (13.2)	54.9 (12.6)	78.2 (71.3)	63.2 (13.4)	64.6 (46.7)
Median (min, max)	44.0 (22.0, 66.0)	56.5 (34.0, 86.0)	59.0 (28.0, 386)	63.5 (45.0, 90.0)	57.0 (22.0, 386)
Bilirubin (µmol/L)					
Mean (SD)	9.29 (2.62)	10.8 (5.63)	12.9 (7.26)	9.48 (3.11)	11.1 (5.79)
Median (min, max)	9.30 (4.40, 12.5)	11.0 (3.70, 22.0)	12.0 (3.50, 37.2)	9.05 (3.90, 16.3)	10.4 (3.50, 37.2)

≈: approximate dose; ALP: alkaline phosphatase; ALT: alanine aminotransferase: AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate: IgG: immunoglobulin G; min: minimum; max: maximum; PK: pharmacokinetic: SD: standard deviation. For participants who had more than 1 dose level, only the highest dose is shown.

Table 18: MG0003: Baseline continuous covariate statistics for participants in the ≈10mg/kg dose group, stratified by dose level (PK-IgG)

Characteristic Statistic	≈10mg/kg 420 mg N=1	≈10mg/kg 560 mg N=25	≈10mg/kg 840 mg N=24	≈10mg/kg 1120 mg N=19	Overall N=69
Age (years)					
Mean (SD)	25.0 (NA)	46.6 (15.9)	54.1 (16.3)	57.3 (15.8)	51.8 (16.6)
Median (min, max)	25.0 (25.0, 25.0)	45.0 (24.0, 79.0)	56.0 (30.0, 81.0)	61.0 (19.0, 77.0)	54.0 (19.0, 81.0)
Body weight (kg)					
Mean (SD)	46.9 (NA)	61.9 (5.64)	82.0 (10.8)	115 (14.5)	83.2 (23.8)
Median (min, max)	46.9 (46.9, 46.9)	63.0 (50.2, 68.6)	82.2 (60.1, 98.7)	113 (100, 156)	76.6 (46.9, 156)
Height (cm)					
Mean (SD)	156 (NA)	166 (6.62)	170 (7.96)	180 (8.69)	171 (9.62)
Median (min, max)	156 (156, 156)	166 (155, 181)	170 (159, 187)	180 (163, 198)	170 (155, 198)
Body mass index (kg/m^2)					
Mean (SD)	19.3 (NA)	22.6 (2.76)	28.4 (3.63)	35.5 (4.51)	28.1 (6.32)
Median (min, max)	19.3 (19.3, 19.3)	22.9 (15.3, 27.5)	28.4 (22.6, 35.0)	34.4 (29.8, 45.5)	27.0 (15.3, 45.5)
eGFR (mL/min/1.73^2)					
Mean (SD)	122 (NA)	103 (19.1)	95.0 (21.0)	93.8 (21.0)	97.9 (20.5)
Median (min, max)	122 (122, 122)	108 (52.9, 128)	95.7 (54.7, 142)	94.4 (47.0, 131)	101 (47.0, 142)
ALT (U/L)					
Mean (SD)	6.00 (NA)	26.0 (35.3)	25.2 (22.8)	26.8 (13.6)	25.7 (25.9)
Median (min, max)	6.00 (6.00, 6.00)	14.0 (8.00, 158)	18.0 (10.0, 120)	25.0 (9.00, 50.0)	17.0 (6.00, 158)
AST (U/L)					
Mean (SD)	14.0 (NA)	21.4 (15.7)	22.0 (11.7)	21.8 (12.9)	21.6 (13.4)
Median (min, max)	14.0 (14.0, 14.0)	17.0 (12.0, 87.0)	18.0 (10.0, 61.0)	17.0 (9.00, 58.0)	17.0 (9.00, 87.0)
ALP (U/L)					
Mean (SD)	43.0 (NA)	54.6 (20.5)	64.2 (19.5)	68.9 (14.6)	61.8 (19.3)
Median (min, max)	43.0 (43.0, 43.0)	46.0 (26.0, 101)	59.0 (46.0, 138)	65.0 (45.0, 91.0)	59.0 (26.0, 138)
Bilirubin (µmol/L)					
Mean (SD)	17.7 (NA)	9.79 (5.19)	11.1 (4.77)	12.6 (5.92)	11.1 (5.33)
Median (min, max)	17.7 (17.7, 17.7)	7.90 (3.90, 24.7)	10.1 (4.00, 19.6)	10.7 (4.70, 30.7)	10.1 (3.90, 30.7)

≈: approximate dose; ALP: alkaline phosphatase; ALT: alanine aminotransferase: AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate: IgG: immunoglobulin G; min: minimum; max: maximum; PK: pharmacokinetic: SD: standard deviation. For participants who had more than 1 dose level, only the highest dose is shown.

Table 19: MG0003: Baseline categorical covariate statistics for participants in the ≈7mg/kg dose group, stratified by dose level (PK-IgG)

	≈7mg/kg 280mg N=7	≈7mg/kg 420mg N=18	≈7mg/kg 560mg N=25	≈7mg/kg 840mg N=14	Overall N=64
Sex					
Male	0 (0%)	1 (5.6%)	13 (52%)	12 (86%)	26 (41%)
Female	7 (100%)	17 (94%)	12 (48%)	2 (14%)	38 (59%)
Race					
Asian	3 (43%)	3 (17%)	3 (12%)	0 (0%)	9 (14%)
White	2 (29%)	11 (61%)	16 (64%)	10 (71%)	39 (61%)
Not reported	2 (29%)	4 (22%)	6 (24%)	4 (29%)	16 (25%)
Baseline steroid					
Absent	2 (29%)	5 (28%)	7 (28%)	7 (50%)	21 (33%)
Present	5 (71%)	13 (72%)	18 (72%)	7 (50%)	43 (67%)

≈: approximate dose; IgG: immunoglobulin G; PK: pharmacokinetic.
For participants who had more than 1 dose level, only the highest dose is shown.

The applicant states that additional simulations evaluating the impact on total IgG reduction and MG-ADL score demonstrated that body weight did not have a meaningful impact on total IgG and no impact on clinical response, which can be explained by sufficient FcRn receptor occupancy being maintained throughout the dosing interval across the weight range. After 6 weekly doses of 560 mg, a 122 kg patient and 46 kg patient were predicted to show a 65.3% and 76.1% decrease from Baseline total IgG, respectively, compared to 73.0% for a 76 kg reference patient. Although total IgG reduction was linearly related to a decrease in MG-ADL score in the model, the minimal effects of body weight on total IgG reduction did not translate to MG-ADL score changes.

Elderly

Based on the PopPK-PD analyses, age (range: 18 to 89 years) or sex (57.5% female) did not impact rozanolixizumab CL/F or V/F or the total IgG or anti-AChR parameters of the PK-PD models.

The number of participants and rozanolixizumab concentration observations in the PK-IgG analysis dataset used for the popPKPD analysis CL0534 are presented by study and age group in the table below.

The final popPKPD model was used to generate individually predicted PK parameters for the participants in the PK-IgG analysis dataset. Summary statistics of apparent clearance at time=0, and model predicted $C_{max,ss}$ and $AUC_{tau,ss}$ after weight-tiered dosing of ≈ 7mg/kg rozanolixizumab, stratified by age group, are presented in Tables 20 - 22.

Non-compartmental analysis (NCA)-based PK parameters could not be generated for participants in the Phase 2 studies TP0001 and MG0002 and Phase 3 studies MG0003 and MG0004 due to the sparse PK sampling scheme used in these studies, and therefore NCA-based descriptive PK statistics are not provided.

Table 20: Number of participants with observations and number of rozanolixizumab and IgG concentration observations by study and age group (PK-IgG)

Study Age group	Rozanolixizumab			IgG		
	Number of participants	Number of observations	Number of observations/ Number of participants	Number of participants	Number of observations	Number of observations/ Number of participants
UP0018						
<65 years	7	35	5.00	23	391	17.00
65-74 years	1	5	5.00	1	17	17.00
All	8	40	5.00	24	408	17.00
UP0060						
<65 years	46	309	6.72	65	960	14.80
MG0002						
<65 years	14	29	2.07	32	428	13.40
65-74 years	1	1	1.00	9	121	13.40
75-84 years	1	1	1.00	2	26	13.00
All	16	31	1.94	43	575	13.40
TP0001						
<65 years	35	70	2.00	49	563	11.50
65-74 years	10	23	2.30	13	154	11.80
75-84 years	2	4	2.00	3	35	11.70
≥85 years	-	-	-	1	14	14.00
All	47	97	2.06	66	766	11.60
MG0003						
<65 years	98	226	2.31	98	226	2.31
65-74 years	23	59	2.57	23	59	2.57
75-84 years	8	28	3.50	8	28	3.50
≥85 years	1	2	2.00	1	2	2.00
All	130	315	2.42	130	315	2.42
MG0004						
<65 years	17	23	1.35	17	23	1.35
65-74 years	4	6	1.50	4	6	1.50
75-84 years	1	2	2.00	1	2	2.00
≥85 years	1	1	1.00	1	1	1.00
All	23	32	1.39	23	32	1.39
UP0106						
<65 years	11	74	6.73	11	74	6.73

Study Age group	Rozanolixizumab			IgG		
	Number of participants	Number of observations	Number of observations/ Number of participants	Number of participants	Number of observations	Number of observations/ Number of participants
All						
<65 years	216	766	3.55	216	766	3.55
65-74 years	36	94	2.61	36	94	2.61
75-84 years	12	35	2.92	12	35	2.92
≥85 years	2	3	1.50	2	3	1.50
All	266	898	3.38	266	898	3.38

Table 21: Apparent clearance at time=0 in the final PK-IgG model stratified by age group.

Apparent clearance (L/day)	<65 years N=334	65-74 years N=56	75-84 years N=19	≥85 years N=3	Overall N=412
Mean (SD)	0.889 (0.356)	1.05 (0.394)	1.09 (0.328)	0.726 (0.398)	0.919 (0.366)
Median (min, max)	0.832 (0.127, 2.52)	0.995 (0.275, 1.98)	1.04 (0.527, 1.68)	0.770 (0.307, 1.10)	0.859 (0.127, 2.52)

IgG=immunoglobulin G; max=maximum; min=minimum PK=pharmacokinetic, SD=Standard deviation.

Table 22: Predicted $C_{max,ss}$ and $AUC_{tau,ss}$ after 6 weekly weight-tiered doses of ≈7mg/kg rozanolixizumab based on individually predicted parameters, stratified by age group (PK-IgG)

Age group	N	$C_{max,ss}$ (mg/L)				$AUC_{tau,ss}$ (mg*day/L)			
		Mean	Median	5th percentile	95th percentile	Mean	Median	5th percentile	95th percentile
<65 years	334	16.0	13.6	1.63	38.8	49.7	37.2	4.14	134
65-74 years	56	14.5	12.4	1.27	36.7	43.6	31.4	3.40	126
75-84 years	19	14.0	12.4	3.29	35.5	42.4	32.1	6.08	117
≥85 years	3	5.68	3.42	1.47	11.5	13.8	8.06	3.28	28.4

≈approximate dose; $AUC_{tau,ss}$ area under the concentration-time curve during a dosing interval at steady state, $C_{max,ss}$ maximum concentration during a dosing interval at steady state; IgG=immunoglobulin G; PK=pharmacokinetic,

Children

No data are available in children.

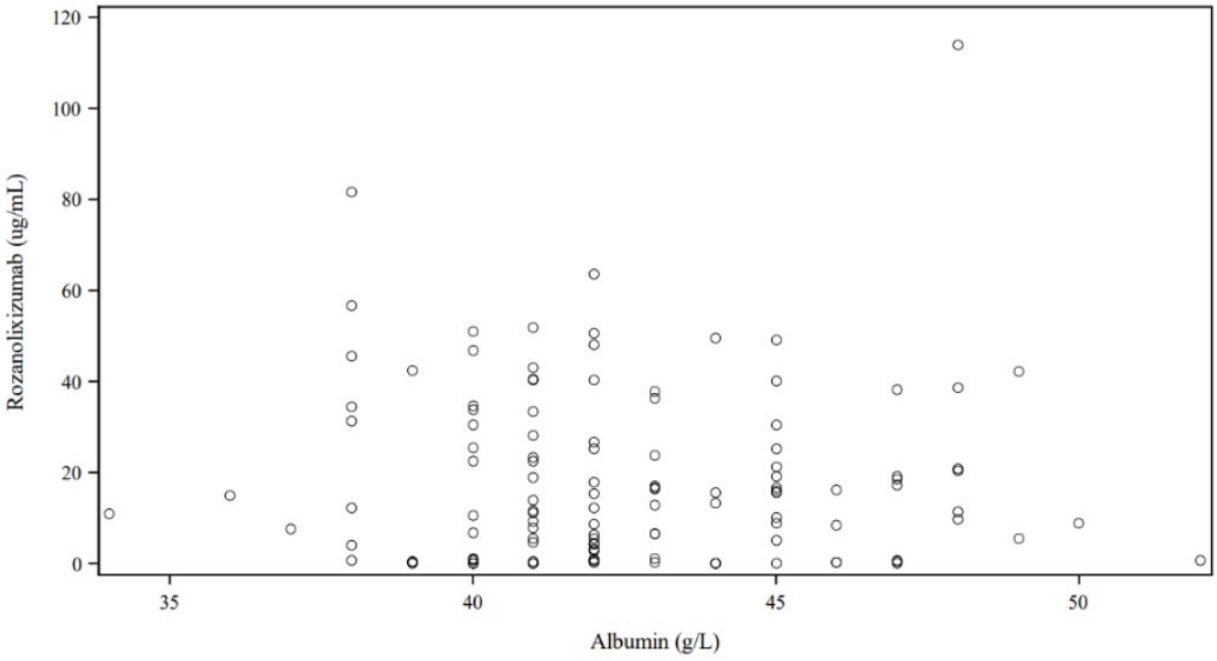
Pharmacokinetic interaction studies

Highly protein-bound drugs

Albumin disposition is known to be mediated by the FcRn receptor. The applicant states that rozanolixizumab has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn and is not expected to have a clinically relevant effect on the disposition of highly protein-bound drugs. In the gMG Phase 3 studies, minimal reductions in albumin were observed during rozanolixizumab treatment. The applicant has not included baseline albumin as a covariate in the rozanolixizumab population PK model. The applicant argued that theoretically, lower serum albumin may indicate that an individual has lower FcRn levels, resulting in higher albumin clearance by catabolism. However, rozanolixizumab clearance is already accelerated relative to other monoclonal antibodies through blockade of FcRn by rozanolixizumab and gMG is not typically associated with hypoalbuminemia. The applicant demonstrates that the pivotal Phase 3 study MG0003, there were no patients with abnormally low albumin at baseline (using the central lab normal range definition). The applicant has conducted a graphical examination of baseline albumin levels versus rozanolixizumab peak plasma

concentrations on Day 3 in MG0003 (Figure 14). There was no evidence of altered Day 3 plasma concentrations of rozanolixizumab in patients with lower baseline albumin levels.

Figure 14: Scatter plot of albumin at baseline vs. individual rozanolixizumab plasma concentrations on Day3, Study MG0003 (SS)



Effect of other drugs on rozanolixizumab

The applicant states that rozanolixizumab is a humanised IgG4 full length antibody and is expected to be catabolised by degradation to small peptides and amino acids, which are expected to be excreted or recycled via pathways in the same manner as endogenous IgG in humans and thus not substrate to hepatic metabolism by e.g., Cytochrome P450.

Pharmacokinetics using human biomaterials

No *in vitro* PK studies involving human biomaterials were conducted. The applicant states that rozanolixizumab is a humanised anti-FcRn mAb. It is neither subject to cytochrome P450 metabolism nor expected to interfere with cytokine levels. Further, rozanolixizumab is not expected to be affected by transporters. Therefore, no in vitro cytochrome P450- or transporter-mediated drug interaction studies were conducted.

In addition, plasma protein binding studies were not conducted, as rozanolixizumab has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn. Albumin levels were monitored in all clinical studies and results from the gMG Phase 3 studies.

2.6.2.2. Pharmacodynamics

Mechanism of action

Rozanolixizumab is a humanised mAb being developed as an inhibitor of the FcRn activity with the aim to reduce the concentration of (pathogenic) IgG in patients with IgG autoantibody-mediated diseases. The MoA of rozanolixizumab is whereby blockade of FcRn leads to enhanced catabolism of IgGs, with the aim to reduce pathogenic autoantibodies in autoimmune diseases.

Primary and Secondary pharmacology

Total serum IgG and IgG subclasses

Dose-dependent decreases in total IgG serum concentrations were observed across the studies in healthy participants and participants with gMG or ITP. The PK-PD relationship between rozanolixizumab exposure and reductions in total IgG was described by indirect response models with the fraction of total FcRn bound to rozanolixizumab increasing total IgG degradation.

In patients with gMG in MG0003, a median total serum IgG reduction of approximately 45% and 53% from Baseline was achieved 7 days after the first dose for weight-tiered doses of ≈7mg/kg and ≈10mg/kg, respectively, and this reduction further increased to approximately 73% and 79%, respectively, following 6-weekly multiple doses of rozanolixizumab. In general, the nadir in total IgG serum concentrations was reached between 21 and 28 days after starting a 6-week treatment cycle. Following the last dose administration, total IgG concentrations recovered towards Baseline levels within approximately 8 weeks, and there was no apparent rebound to above baseline levels observed across studies. This recovery period is consistent with an estimated IgG half-life of 18.8 days.

Total IgG data from MG0003 and MG0004 and interim data from MG0007 were pooled to investigate the effect of Treatment Cycles of rozanolixizumab on the PD profile (Pool S2, see Table 23).

Table 23: Maximum percentage changes from baseline in total IgG, anti-AChR autoantibodies, and anti-MuSK autoantibodies by cycle following ≈7mg/kg or ≈10mg/kg SC dose of rozanolixizumab in participants with gMG (Pool S2)

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
Treatment Timepoint	Baseline	Max % change from Baseline	Baseline	Max % change from Baseline	Baseline	Max % change from Baseline	Baseline	Max % change from Baseline
RLZ ≈7mg/kg (N=94)								
Total IgG (g/L), Median [N]	9.660 [91]	-70.87 [89]	8.295 [66]	-68.63 [64]	8.490 [47]	-66.91 [45]	8.005 [40]	-67.58 [38]
Anti-AChR autoantibodies (nmol/L), Median [N]	5.030 [77]	-72.81 [72]	6.620 [50]	-63.26 [42]	11.100 [33]	-52.21 [28]	11.650 [22]	-56.00 [15]
Anti-MuSK autoantibodies (nmol/L), Median [N]	15.400 [7]	-28.88 [7]	53.750 [6]	-46.11 [6]	74.300 [4]	-61.91 [4]	-	-
RLZ ≈10mg/kg (N=94)								
Total IgG (g/L), Median [N]	9.140 [91]	-78.14 [90]	7.630 [70]	-71.17 [69]	8.345 [62]	-72.56 [60]	8.080 [50]	-67.13 [47]
Anti-AChR autoantibodies (nmol/L), Median [N]	9.160 [75]	-75.00 [73]	14.400 [55]	-69.44 [47]	13.200 [44]	-67.11 [33]	15.150 [36]	-53.45 [30]
Anti-MuSK autoantibodies (nmol/L), Median [N]	40.200 [5]	-57.76 [4]	-	-	-	-	-	-
RLZ Total (N=188)								
Total IgG (g/L), Median [N]	9.445 [182]	-75.06 [179]	8.000 [136]	-70.05 [133]	8.470 [109]	-70.03 [105]	8.080 [90]	-67.20 [85]
Anti-AChR autoantibodies (nmol/L), Median [N]	6.935 [152]	-73.29 [145]	8.370 [105]	-67.33 [89]	12.200 [77]	-62.95 [61]	14.600 [58]	-54.57 [45]
Anti-MuSK autoantibodies (nmol/L), Median [N]	24.250 [12]	-44.32 [11]	33.650 [8]	-51.49 [7]	37.600 [5]	-58.12 [5]	90.300 [3]	-47.00 [3]

The PD profile observed during repeated cyclic treatment was consistent with that seen in MG0003. Median maximum reductions in total IgG for rozanolixizumab total (≈7mg/kg and ≈10mg/kg combined) were 75% for Cycle 1, 70% for Cycle 2, 70% for Cycle 3, and 67% for Cycle 4.

Changes from Baseline for all IgG subclasses were generally consistent with the results for total IgG, with median maximum reductions of 75.3% and 80.6% for IgG1, 66.8% and 72.9% for IgG2, 78.4%

and 85.1% for IgG3, and 60.7% and 67.6% for IgG4 after rozanolixizumab doses of ≈7mg/kg and ≈10mg/kg in MG0003.

Disease-specific autoantibodies

Median maximum reductions in anti-AChR autoantibodies for rozanolixizumab total (≈7mg/kg and ≈10mg/kg combined) were 73% for Cycle 1, 67% for Cycle 2, 63% for Cycle 3, and 55% for Cycle 4. Median maximum reductions in anti-MuSK autoantibodies for rozanolixizumab total (≈7mg/kg and ≈10mg/kg combined) were 44% for Cycle 1, 51% for Cycle 2, 58% for Cycle 3, and 47% for Cycle 4.

In the PopPK-tIgG analysis, plots of percent change from Baseline MG-specific autoantibodies versus percent change from Baseline total IgG show a high correlation for anti-AChR autoantibodies, suggesting that the effects of percent change in total IgG on MG-ADL score could be expected also for percent change in anti-AChR autoantibodies. The correlation between total IgG and anti-MuSK autoantibodies was weaker. Baseline concentrations of disease-specific IgG were not found to be statistically significant covariates for the PK-tIgG model.

The PK-PD relationships between rozanolixizumab exposure and reductions in anti-AChR and anti-Musk autoantibodies were described by indirect response models with the fraction of total FcRn bound to rozanolixizumab increasing the disease-specific autoantibody degradation. The final PK-tIgG-AChR model provided an adequate description of the observed longitudinal plasma rozanolixizumab concentrations, total serum IgG, and anti-AChR concentrations in anti-MuSK negative participants. The PK-tIgG-AChR-MuSK model was developed based on limited anti-MuSK data and anti-MuSK related parameters were estimated with high uncertainty in the final model. For this reason, the final PK tIgG AChR-MuSK model was not deemed fit for the purpose of simulating the time course of anti-MuSK and MG-ADL in the evaluation of a 2-fixed dose regimen in comparison to weight-tiered dosing regimens.

Antidrug Antibodies

In the pool of placebo controlled MG0003 and long-term extension MG0007 data, the prevalence of pre-existing ADA was low (1.2%). Treatment-emergent ADA occurred as early as 14 days after the first infusion, and cumulative counts increased over time.

With the chronic weekly treatment regimen of up to 52 weeks of rozanolixizumab in MG0004, the treatment-emergent ADA incidence was 53.6% up to the individual Final Visit for the entire population (i.e., a maximum of 52 weeks of treatment).

Data from the 3 Phase 3 gMG studies were also used to assess the influence of ADA on clinical outcomes. The PK of rozanolixizumab was impacted in the presence of Nab, with a 17% and 24% lower maximum plasma concentration and overall exposure (AUC) in Nab positive compared with ADA negative study participants. The changes in the PK of rozanolixizumab resulted in small changes in the total IgG response that were not clinically relevant; similar results were observed in the pooled analysis of MG0003 and MG0007 data. The applicant states that there was no impact of immunogenicity on the efficacy (MG-ADL score) or safety (including immunogenicity-related reactions) of rozanolixizumab through 5 treatment cycles.

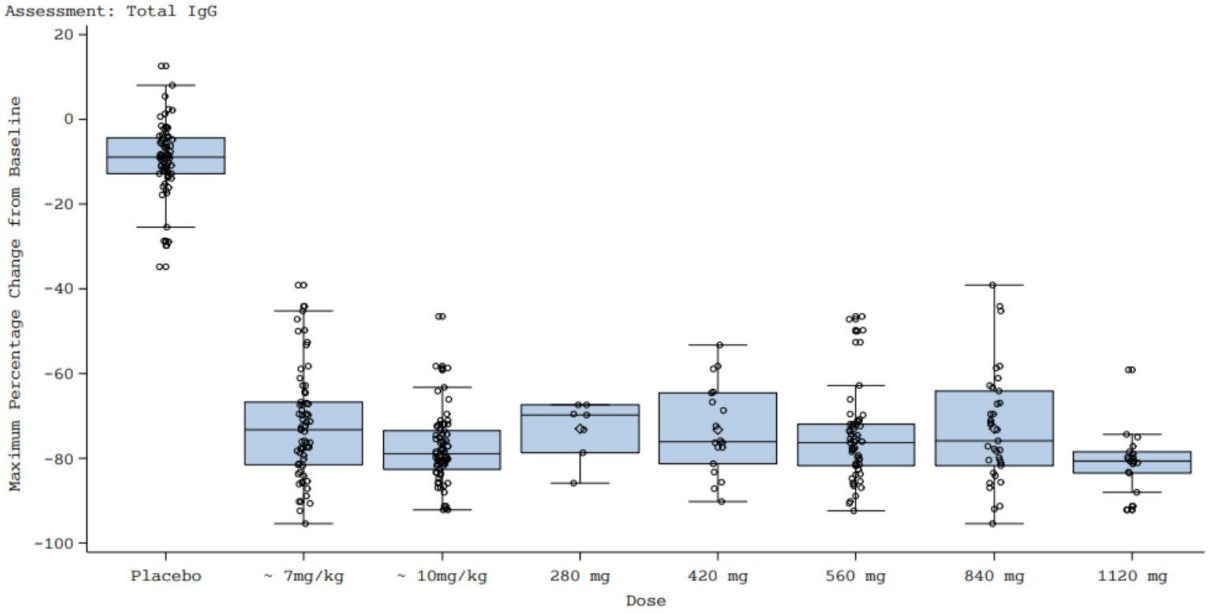
Pharmacodynamics by administered fixed dose

Total serum IgG

In MG0003, the total serum IgG mean time profiles were similar across the administered fixed dose range (280mg, 420mg, 560mg, 840mg, and 1120mg). Mean maximum percentage changes from Baseline for total serum IgG were generally similar across the administered fixed dose. The median maximum percentage change from Baseline was slightly lower for the 280mg dose compared with the

higher doses (Figure 15); variability was high. In MG0007, median maximum percentage changes from Baseline for total serum IgG were generally similar across the administered fixed dose range throughout all treatment cycles.

Figure 15: Boxplot of maximum percentage change from Baseline in total IgG (up to Day 43) by administered dose in MG0003 (Safety Set)



~=approximate dose; IgG=immunoglobulin G

Secondary pharmacology

A dedicated corrected QT (QTc) prolongation study was not conducted as rozanolixizumab have a low likelihood of direct ion channel interaction. This is accepted. The effect of rozanolixizumab on QT-interval was assessed within individual clinical studies. There were no participants in the gMG Phase 3 studies MG0003 and MG0007 with Fridericia corrected QT interval (QTcF) ≥500ms or QTcF change from Baseline ≥60ms.

Pharmacodynamic interactions with other medicinal products or substances

The effect of concomitant use of corticosteroids was evaluated in the PopPKPD analyses. Baseline steroid usage was identified as a statistically significant covariate on Baseline total IgG and E_{max}, leading to a predicted maximum IgG reduction of 77.6% in gMG patients on steroids compared to 73.0% in gMG patients not on steroids. Baseline steroid usage was also tested as a covariate in the MG-ADL score model but did not affect any of the model parameters.

Human IV or SC immunoglobulin treatment may interfere with the endosomal FcRn recycling mechanism of mAb and thereby decrease serum concentrations of rozanolixizumab.

Vaccination during rozanolixizumab treatment has not been studied and the response to any vaccine is unknown. Because rozanolixizumab causes a reduction in IgG levels, vaccination with live-attenuated or live vaccines is not recommended during treatment with rozanolixizumab.

Relationship between plasma concentration and effect

The effect of rozanolixizumab on MG-ADL score was assumed to be exerted through the decline in total IgG or anti-AChR, expressed as relative change from baseline in percent. The correlation between anti-MuSK and MG-ADL was also described by a direct response model but no placebo effects could be described, and no covariate effects were tested due to the limited number of MuSK positive participants and large variability in the anti-MuSK concentrations.

2.6.3. Discussion on clinical pharmacology

The clinical pharmacology programme includes PK, PD, and immunogenicity data from 8 completed and ongoing clinical studies. These include 3 Phase 1 studies: a FIH study in healthy participants (UP0018), a safety, tolerability, PK, and PD study of rozanolixizumab in Japanese, Chinese, and Caucasian healthy participants (UP0060), and a safety, tolerability, PK, and PD study of rozanolixizumab administered via manual push versus syringe driver to healthy participants.

An exploratory PopPKPD model was developed on observed PK and total IgG data from 1 Phase 2 study and 2 Phase 1 studies. The purpose of the model was to support dose selection for the Phase 3 studies.

A second PopPKPD model was developed on observed PK and total IgG data from 3 Phase 1 studies, 2 Phase 2 studies, and 2 Phase 3 studies, as well as MG-ADL score data from MG0003. The models were extended with disease-specific autoantibody data from 1 Phase 2 study and 2 Phase 3 studies in gMG.

The final popPKPD model consisted of three sub-models, describing the longitudinal plasma rozanolixizumab concentrations, serum total IgG, and anti-AChR concentration, respectively. The PK-tIgG model was a one compartment disposition model with first-order absorption and a first-order elimination from the central compartment, in addition to a TMDD using the quasi-equilibrium approximation, while an indirect-response model described the turnover of IgG. A large proportion of rozanolixizumab plasma concentrations were below the lower limit of quantification (LLOQ) and excluded during the model development but based on goodness-of-fit (GOF) graphics and VPCs there were no signs of misspecification due to ignoring samples below the LLOQ when performing parameter estimation. The PK-tIgG model included the following statistically significant covariate effects: body weight on FcRn independent CL/F, V/F, and baseline IgG, presence of ADA/Nab on FcRn independent CL/F, formulation on MAT, ITP patient on V/F, and baseline steroid use on baseline IgG and E_{max}. In general, both fixed and random effects were estimated with adequate precision. The stability of the final model and CIs of model parameters were evaluated by a non-parametric bootstrap analysis. Out of 425 model runs, 310 (72.9%) had successful minimisation and 115 (27.1%) were terminated due to rounding errors, which indicates a relatively unstable model. All parameters were associated with good accuracy except for the 2 parameters corresponding to the effect of ADA and Nab on CL/F. η-shrinkage was low on IgG model parameters (range: 2.13%-15.5%) but moderate-to-high on PK model parameters (range: 23.5%-63.1%). PcVPCs for PK suggests adequate predictive performance of the model in all treatment groups and dosing regimens. However, pcVPCs of PK vs. body weight suggests slight overprediction across the body weight range. The overall IgG-model performance was observed based on GOF-plots and pcVPCs. External validation of MG00007 data suggested the final PK-IgG model can adequately describe trends in MG0007 data.

The final tIgG-MG-ADL model was a direct response model with a placebo effect. The effect of rozanolixizumab was assumed to be exerted through the decline in total IgG, expressed as relative change from baseline in percent. Parameters were estimated with adequate precision (%RSE). Eta-shrinkage was low on MG-ADL score baseline (8%), high on E_{maxMG} (34%) and moderate on placebo (27%). In general, IIV and RUV were large (%CV range: 38%-323%). Very few subjects above body weights of 100 kg were included in the data set and the predictive performance of the model in patients above 100 kg is questionable.

The final model for anti-AChR effects on MG-ADL was a direct response model with the time-dependent placebo effects and the anti-AChR effects reducing the MG-ADL score. Parameters were estimated with adequate precision except for MGFA disease class on MG-ADL baseline (%RSE = 44%). Shrinkage was low on MG-ADL baseline but moderate on $E_{max,MG}$ and Placebo (29.7% and 27.6%, respectively). GOF-plots and pcVPCs suggests an adequate model fit and predictive performance. IIV and RUV were large (%CV range: 38%-253%).

Two different formulations were used during clinical development: the liquid formulation and the lyophilised formulation, with the liquid formulation being the proposed commercial formulation. No formal bioequivalence or bioavailability study has been conducted. The lyophilised formulation was used in Phase 2 studies MG0002 and TP0001, In MG0002 all plasma concentrations were below the limit of quantification due to the sampling schedule used, therefore quantifiable PK data for the lyophilised formation are only available ITP patients. In population PK-PD analysis CL0534, the lyophilised formulation was tested as a covariate on MAT and was found to have a shorter MAT than the liquid formulation leading to a predicted 111% and 105% higher rozanolixizumab steady state C_{max} and AUC, respectively, after 6 weekly doses of 560mg. Immune thrombocytopenia patients were estimated to have an 86% lower $Cm_{ax,ss}$ and 85% lower AUC_{ss} compared to healthy participants and gMG patients. Given that the covariate effects of ITP patient population and lyophilised formulation were found to result in opposite changes in predicted exposure, it is possible that the popPKPD analysis was not able to correctly identify the covariate relationships for formulation and patient population, which may have resulted in exaggerated effects for both covariates.

For a typical 76kg study participant (median body weight in the dataset), the estimated linear FcRn independent V/F was 6.6L. The applicant argued that estimates for V from PK-PD analysis are in good concordance with the estimate of 6.6 L for V/F from the final popPKPD model CL0534, considering an estimated F of 67%. This can be accepted.

The population estimate for the FcRn independent CL/F was 0.89L/day for a typical gMG patient of 76kg. An estimate of CL was obtained in the exploratory popPKPD analysis CL0460. In this analysis, CL was estimated to be 1.1L/day, which would equate to a CL/F value of 1.65L/day considering an estimated F of 67%. For the product information, the applicant proposes using the estimate for CL/F from the final population PK-PD analysis as this is the estimate obtained in the target gMG population, which is accepted. It was not possible to calculate half-life for unbound rozanolixizumab in plasma due to the nonlinear PK profile of rozanolixizumab at therapeutic doses. This information has been adequately addressed in the SmPC.

A dedicated renal impairment study has not been conducted. In the PopPKPD analysis, which included participants with mild and moderate renal impairment, eGFR (range: 38.2 to 161Ml/min/1.73m2) did not show any significant impact on rozanolixizumab CL/F. The SmPC adequately states that there is limited safety and efficacy data is available in patients with mild to moderate renal impairment and no data is available in patients with severe renal impairment. However, no dose adjustment is considered necessary as the PK of rozanolixizumab are unlikely to be affected by renal impairment (section 4.2 of the SmPC).

No data is available to allow identification and classification of hepatically impaired patients based on the Child-Pugh criteria. This information has been adequately addressed in the SmPC**.**

Body weight was predicted to have the largest impact on rozanolixizumab exposure with an 85% lower $C_{max,ss}$ and 85% lower AUC_{ss} in a patient with the 97.5^{th} percentile of the baseline covariate value (122kg) and a 228% higher $C_{max,ss}$ and 398% higher AUCss in a patient with the 2.5^{th} percentile of the baseline covariate value (46kg) relative to the reference patient of 76kg. The applicant has provided predicted rozanolixizumab PK profiles by dose. There is substantial variability in predicted rozanolixizumab PK profiles within and across the treatment groups and weight tiers. The applicant states that a low number of participants (n) in each dose group may have contributed to the extremely large variability in PK. Furthermore, rozanolixizumab undergoes significant TMDD because of binding to FcRn and accelerating the clearance of IgG including rozanolixizumab itself, which leads to a short duration of plasma exposure. Finally, body weight is predicted to have the largest impact on rozanolixizumab plasma exposure. However, despite inclusion of body weight and other covariates in the population PK model, a considerable part of the interindividual variability in rozanolixizumab PK remains unexplained. The

applicant argued that and that the PK variability of rozanolixizumab is substantially greater than the PD variability. Furthermore, the applicant argued that differences in unbound plasma rozanolixizumab exposure will not have a significant impact on total IgG or clinical response as long as FcRn saturation remains sufficient to exert its effect. The applicant's argumentation can be followed.

The applicant states that additional simulations evaluating the impact on total IgG reduction and MG-ADL score demonstrated that body weight did not have a meaningful impact on total IgG and no impact on clinical response, which can be explained by sufficient FcRn receptor occupancy being maintained throughout the dosing interval across the weight range. However, these results are explorative and depends highly on the robustness of the model and can therefore only be supportive to the efficacy and safety evaluations.

The applicant initially proposed two fixed dose regimen [420mg if body weight ≥35kg to <50kg and 560mg if body weight≥50kg]. This was considered a major concern as this regimen does not fully reflect the studied dosing regimens in the phase 2 (mg/kg dosing) and the phase 3 trials (5 flat doses according to 4 weight tiers). Due to concerns regarding the PK/PD, efficacy and safety, the applicant was requested to justify their proposal. The applicant acknowledged this concerned and proposed to switch to the weight-tiered dosing as used in the Phase 3 clinical studies, selecting the lower dose of ≈7mg/kg as no incremental benefit was observed with the higher dose. The CHMP agreed on the updated 4 weight-tiers proposal [280mg if body weight ≥35kg to <50kg; 420mg if body weight ≥50kg to <70kg; 560mg if body weight ≥70kg to <100kg and 840mg if body weight ≥100kg].

Age (range: 18 to 89 years) or sex (57.5% female) did not impact rozanolixizumab CL/F or V/F or the total IgG or anti-AChR parameters of the PK-PD models.

The available data in the elderly is limited but the popPK analysis did not reveal a clinically significant impact of age. No dose adjustment is required as indicated in section 4.2 of the SmPC. No data are available in children. The applicant has proposed the following information in the SmPC: "The safety and efficacy of rozanolixizumab in children below the age of 18 years have not been established. No data are available.". This is endorsed.

Albumin disposition is known to be mediated by the FcRn receptor. The applicant states that rozanolixizumab has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn and is not expected to have a clinically relevant effect on the disposition of highly protein-bound drugs. In the gMG Phase 3 studies, minimal reductions in albumin were observed during rozanolixizumab treatment. The applicant has not included baseline albumin as a covariate in the rozanolixizumab population PK model. The applicant demonstrates that the pivotal Phase 3 study MG0003, there were no patients with abnormally low albumin at baseline. Furthermore, there was no evidence of altered Day 3 plasma concentrations of rozanolixizumab in patients with lower baseline albumin levels. This argumentation can be followed.

The applicant did not evaluate the effect of highly protein-bound drugs on the PK of rozanolixizumab. There are no known reports whereby the PK of mAb was altered in the presence of highly protein-bound drugs. This can be agreed.

A correlation between total IgG and anti-MuSK autoantibodies was questioned. The applicant acknowledged the weaker correlation between total IgG and anti-MuSK autoantibodies as compared to anti-AChR autoantibodies but focuses on the IgG4 being lowered by the treatment. Please see further discussion on the anti-Musk positive seropositive patients under efficacy discussion.

The applicant states that there was no impact of immunogenicity on the efficacy (MG-ADL score) or safety (including immunogenicity-related reactions) of rozanolixizumab through 5 treatment cycles. Events of treatment failure was not found related to immunogenicity.

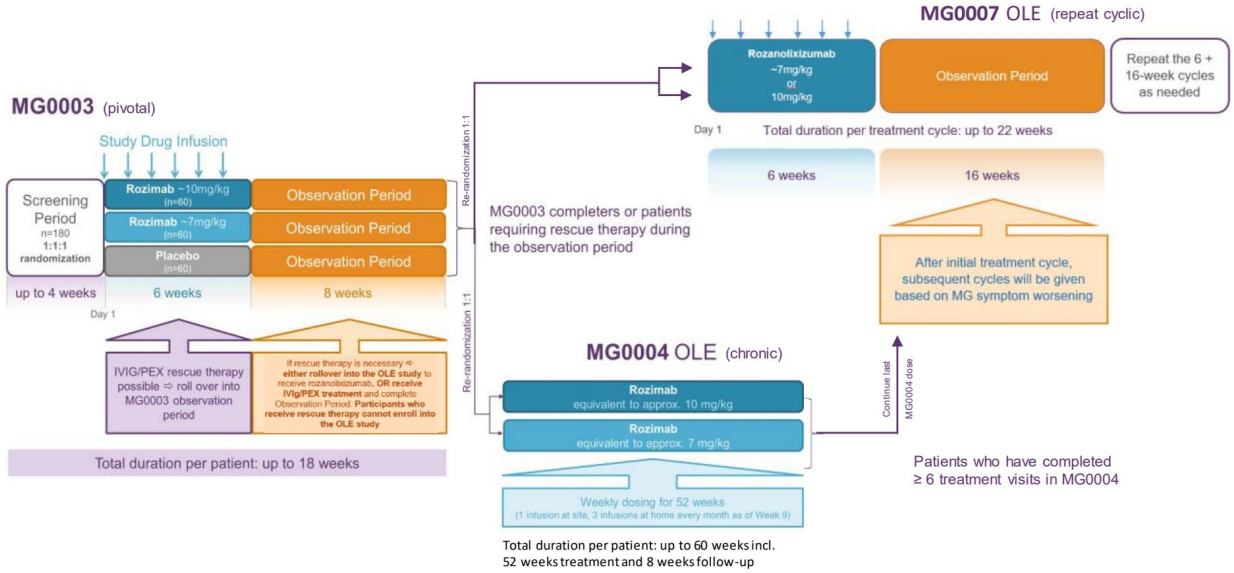
2.6.4. Conclusions on clinical pharmacology

The rozanolixizumab clinical pharmacology programme has characterised the PK, PD, immunogenicity, and dose-exposure-response properties of rozanolixizumab in healthy study participants and study participants with gMG. A major objection was raised on the proposed 2-fixed dosing regimen in addition to several other concerns. All issues have been resolved supporting the 7 mg/kg dosing regimen.

2.6.5. Clinical efficacy

The evaluation of efficacy is primarily based on the Phase 3 placebo-controlled study, MG0003 in moderate to severe gMG. To assess the efficacy of MG symptom-driven repeat 6-week cyclic treatment with rozanolixizumab, MG0007 data (cutoff 08 Jul 2022) and limited data from MG0004 (first 6 weeks) are integrated with MG0003 for the pooled analyses (see tabular overview of clinical studies above and Figure 16).

Figure 16: Rozanolixizumab phase 3 development programme in patients with gMG



~=equivalent dose; IVIg=intravenous immunoglobulin G; OLE=open-label extension; PEX=plasma exchange; Rozimab=rozanolixizumab

2.6.5.1. Dose response study

The FIH study in healthy participants receiving IV or SC rozanolixizumab (UP0018), provided evidence that the SC route is the appropriate route of administration for multiple dosing of rozanolixizumab up to 7mg/kg for future clinical studies.

Subsequent efficacy and safety results from a Phase 2a study (MG0002) supported the Phase 3 development for rozanolixizumab for gMG. A single pivotal, placebo-controlled Phase 3 study was conducted (MG0003) that had provided evidence of the efficacy and safety of rozanolixizumab for the treatment of moderate to severe gMG. Two doses (≈7mg/kg and ≈10mg/kg) were chosen for MG0003. The ≈7mg/kg dose was selected to replicate and confirm clinical improvements in MG-ADL achieved in MG0002, and the ≈10mg/kg dose was introduced to assess if additional benefit could be gained through either a greater magnitude of effect or shorter time to onset of clinical response, while maintaining a positive benefit-risk profile.

Table 24: gMG phase 3 dose levels and weight tiers and proposed fixed doses.

Body weight	Rozanolixizumab doses in Phase 3 programme		Proposed fixed doses	Primary evidence to support dose
	≈7mg/kg	≈10mg/kg		
≥35 to <50kg	280mg	**420mg**	420mg	MG0003 and MG0007 clinical efficacy and safety
≥50 to <70kg	420mg	**560mg**	560mg	MG0003 and MG0007 clinical efficacy and safety
≥70 to <100kg	**560mg**	840mg		MG0003 and MG0007 clinical efficacy and safety
≥100kg	840mg	1120mg		Modelling and simulation

≈=approximate dose

Based on the positive benefit-risk profile of the studied weight-tiered doses of ≈7mg/kg and ≈10mg/kg rozanolixizumab in the Phase 3 pivotal study in gMG, a 2-fixed dosing regimen of rozanolixizumab is initially proposed for labelling in gMG patients: 560mg for patients weighing ≥50kg and 420mg for patients weighing ≥35 to <50kg (Table 24).

The proposed fixed doses for labelling are based on observed clinical efficacy and safety data in the placebo-controlled study (MG0003) and OLE studies, as well as the model-informed analyses of rozanolixizumab exposure, total IgG and anti-AChR autoantibody levels, and MG-ADL.

Analyses by administered fixed dose in MG0003 and MG0007 show that the overall efficacy profiles are generally similar across fixed doses. The safety profile was generally similar across the 5 administered fixed doses in MG0003. With repeated cyclic treatment in MG0007, the 840mg and 1120mg doses showed a trend for a higher incidence of treatment-emergent adverse events (TEAEs) compared with the 420mg and 560mg doses.

For the 2 proposed fixed doses of 420mg (<50kg) and 560mg (≥50kg to <100kg), results from the efficacy and safety analyses were consistent with those for the weight-tiered doses of ≈7mg/kg and ≈10mg/kg. In addition, the model-informed simulations show that the 2-fixed and weight-tiered dosing regimens are expected to perform similarly in terms of exposure, total IgG and anti-AChR reduction, and MG-ADL response (Figure 17).

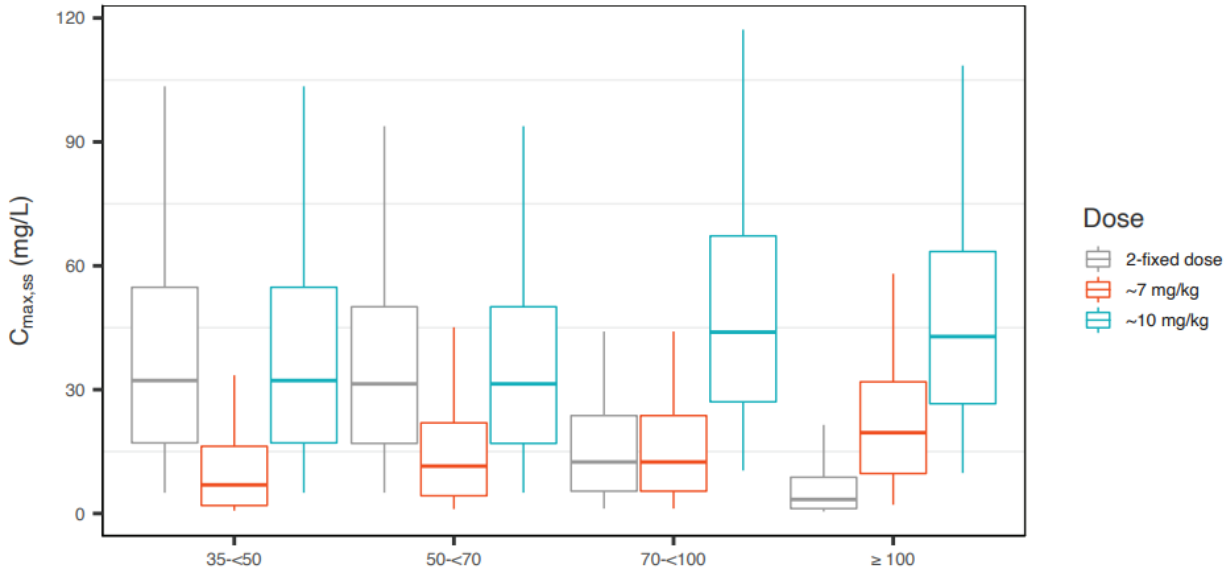
The proposed fixed doses in each weight tier are supported as follows:

• 420mg (≥35 to <50kg): No multiple dose safety data for 560mg are available for patients in the lower (≥35 to <50 kg) body weight tier, and therefore, the highest evaluated dose of 420mg is proposed for this body weight tier. A tendency for lower clinical improvement in participants treated with the 280mg dose was observed. The efficacy and safety profile of the 420mg dose was consistent with the ≈7mg/kg and ≈10mg/kg treatments groups.

• 560mg (≥50 to <100kg): The 560mg dose showed improvements in all efficacy scores across the ≥50 to <70kg and ≥70 to <100kg weight groups, supporting the use of the 560mg dose across both weight bands. The safety profile of the 560mg (≥50 to <100kg) fixed dose was consistent with the ≈7mg/kg and ≈10mg/kg treatments groups.

• 560mg (≥100kg): All participants in this weight tier received doses >560mg (840mg or 1120mg) in the Phase 3 programme and thus it is assumed that the safety profile of a 560mg dose in patients ≥100kg should be acceptable. Model-informed predictions of rozanolixizumab exposure, total IgG and anti-AChR autoantibody levels, and MG-ADL provide evidence that efficacy is maintained with a 560mg dose in this weight tier (Table 25).

Figure 17: Box plots of predicted $C_{max,ss}$ following SC administration of the 2-fixed dose and weight-tiered ≈7mg/kg and ≈10mg/kg doses, stratified by weight tier



≈: approximate dose; Q1W=once a week; SC: subcutaneous.
Note: Doses for the 2-fixed dose regimen are 420mg in patients weighting <50kg and 560mg in patients weighing ≥50kg one a week. For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈7mg/kg: 35 to <50kg: 280mg, 50 to <75kg: 420mg, 70 to <100kg:560mg; ≥100kg:840mg; for ≈10mg/kg: 35 to <50kg: 420mg, 50 to <75kg: 560mg, 70 to <100kg:840mg; ≥100kg:1120mg).
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 75th percentiles, whiskers extend between 5th and 95th Percentiles.

Table 25: 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

≈: approximate dose; AChR=acetylcholine receptor; gMG=generalised myasthenia gravis; IgG=immunoglobulin G; MG-ADL=myasthenia gravis of daily living; PK=pharmacokinetic: Q1W=once a week.
Note: Doses for the 2-fixed dose regimen are 420mg in patients weighting <50kg and 560mg in patients weighing ≥50kg Q1W. For the weight-tiered regimen, fixed doses were defined across 4 body weight tiers (for ≈7mg/kg: 35 to <50kg: 280mg, 50 to <75kg: 420mg, 70 to <100kg:560mg., ≥100kg:840mg; for ≈10mg/kg: 35 to <50kg: 420mg, 50 to <75kg: 560mg, 70 to <100kg:840mg., ≥100kg:1120mg).
Note: Six weekly doses were simulated for each dosing regimen.
Note: MG-ADL score predictions presented are based on total Ig/MG/DL model. Predictions based on AChR-MG-ADL were similar.

2.6.5.2. Main study

MG0003: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients with Generalized Myasthenia Gravis

Methods

MG0003 was a multicentre randomised, double-blind, placebo-controlled, 3-arm repeat dose study evaluating efficacy and safety of 2 doses of rozanolixizumab and matching placebo in adult participants with gMG experiencing moderate to severe symptoms and being considered for additional treatment such as IVIg or PEX (Figure 16).

The study consisted of a screening period of up to 28 days (to account for central laboratory testing turn-around time), a 6-week treatment period (with randomisation on day 1) and an 8-week blinded observation period that began a week after the last infusion. The maximum duration of the study per study participant was up to 18 weeks.

The sequence and movement of participants through study phases were as follows:

All study participants who completed the 6-week treatment period were to rollover into an 8-week observation period. All eligible study participants who completed the observation period were invited to be re-randomised into the OLE MG0004 study (a randomised, long-term (52-week chronic treatment)) or its replacement OLE MG0007 study (6-week treatment cycles based on MG worsening) to either active dose group 1 or 2.

Study participants who experienced disease worsening during the 6-week treatment period (e.g, an increase of 2 points on the MG-ADL or 3 points on the quantitative MG [QMG] scale between 2 consecutive visits) were considered for rescue therapy (IVIg or PEX) at the discretion of the Investigator. Study participants who needed rescue therapy during the 6-week treatment period were to receive IVIg or PEX and complete any subsequent visit(s). No further infusions of rozanolixizumab were administered after initiation of rescue therapy. Once the participant completed Visit 10, they were moved into the 8-week Observation Period.

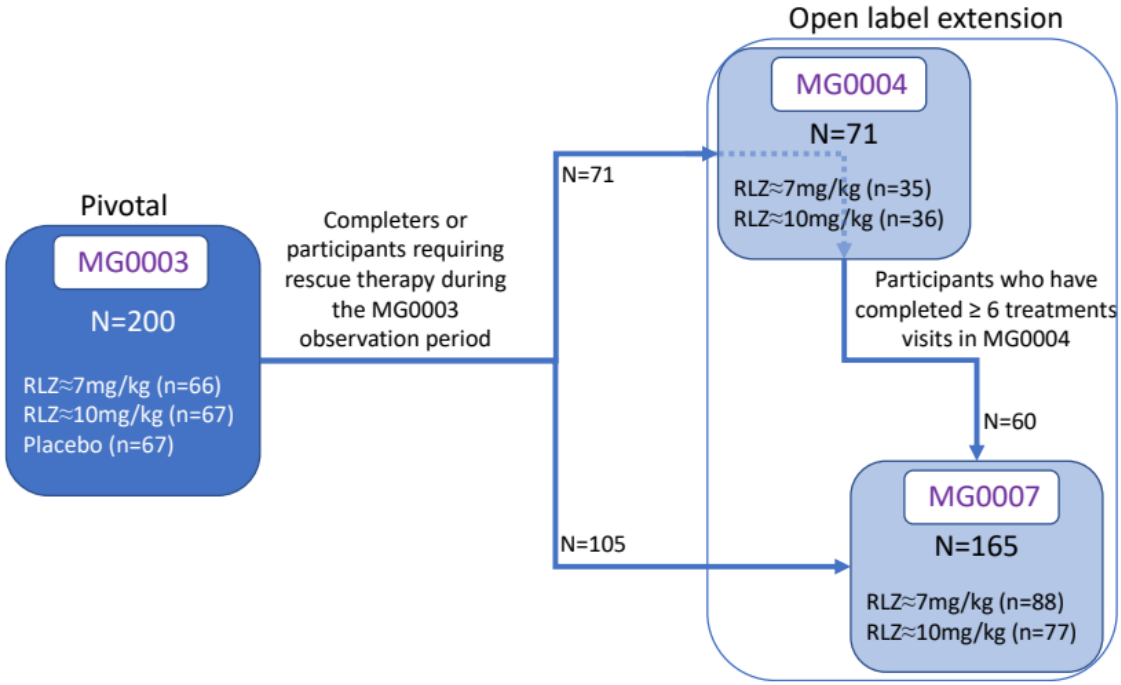
Study participants who completed the treatment period and required initiation of rescue therapy after they started the 8-week observation period, may have either opted to receive IVIg or PEX or complete the End of Study (EOS) Visit and immediately rollover into an OLE study where the participant received rozanolixizumab. Study participants who opted to receive IVIg or PEX were to complete any remaining visits in the Observation Period and were not invited to join an OLE study.

Study participants who did not complete the 6-week treatment period because they needed rescue therapy and required initiation of a second course of rescue therapy while in the 8-week observation period could have rolled over into an OLE study if a minimum of 2 weeks had lapsed since completion of

the last IVIg or PLEX administration. The EOS Visit must have been completed before enrolling into an OLE study. Alternatively, they could have been treated with IVIg or PEX. Study participants who opted to receive IVIg or PEX were to complete any remaining visits in the Observation Period and were not invited to join an OLE study.

Study participants who discontinued investigational medicinal product (IMP) for any reason other than requiring rescue therapy were not to be eligible for enrolment into an OLE study.

Figure 18: Flow of study participants in the Phase 3 studies



≈=approximate dose; RLZ=rozanolixizumab Note: Participants requiring rescue therapy and rolling over to the open label extensions did not receive IVIg/PLEX but rozanolixizumab.

- **Study Participants**

The participants were randomised from 81 sites in 17 countries in North America, Europe, and Asia. Geographic regions and countries were categorised as follows:

• Asia (excluding Japan): Taiwan

• Europe: Belgium, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, Georgia, Hungary, Italy, Poland, Russian Federation, Serbia

• North America: Canada, United States

• Japan: Japan

Inclusion criteria:

Male and female study participants must have been ≥18 years of age; have had a documented diagnosis of gMG at Visit 1, based on the study participant's history and supported by previous evaluations; have had a confirmed positive record of autoantibodies against AChR or MuSK at screening (Visit 1); have had MGFA Class II to IVa at Visit 1; have had a MG-ADL score of at least 3 (with ≥3 points from a nonocular symptom) and a QMG score of at least 11 at Visit 1 and at Baseline (Visit 2); have had body weight ≥35kg at Visit 1: and had been considered for additional treatment such as IVIg or PEX by the Investigator.

Exclusion criteria:

Study participants were not permitted to enrol in the study if any of the following criteria were met at Visit 1 (unless otherwise indicated):

1. Study participant had any medical or psychiatric condition that, in the opinion of the Investigator, could have jeopardised or would have compromised the study participant's ability to participate in this study.

2a. Study participant had a history of alcohol use disorder or other substance use disorder (as per the Diagnostic and Statistical Manual of Mental Disorders-5) within 12 months prior to Visit 1.

3. Study participant had a known hypersensitivity to any components of the study medication or comparative drugs as indicated in the protocol.

4a. Study participant had a known history of hyperprolinaemia, given that L-proline is a constituent of the rozanolixizumab Formulation.

5. Study participant had a clinically relevant active infection (e.g., sepsis, pneumonia, or abscess) in the opinion of the Investigator, or had a serious infection (resulting in hospitalisation or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of study medication.

6. Study participants with a known tuberculosis infection, at high risk of acquiring tuberculosis infection, latent tuberculosis infection, or current/history of nontuberculous mycobacterial infection were excluded.

7. Study participant had previously received rozanolixizumab.

8. Study participant had received a live vaccination within 8 weeks prior to Visit 2 or intended to have a live vaccination during the study or within 8 weeks following the final dose of study medication.

9a. Study participant had been treated with prohibited immunosuppressants, biologics, and other therapies within timeframe shorter than the indicated treatment-free period. Patients were excluded if they had received immunosuppressants (cyclophosphamide within 6 months; pimecrolimus within 4 weeks; vinca alkaloids within 12 weeks), biologics (rituximab, ocrelizumab, inebilizumab within 6 months or 12 months if B-cells did not return to normal range; abatacept, belimumab, golimumab, natalizumab, ofatumumab, veltuzumab within 6 months; eculizumab within 3 months; other biologics within 3 months or within 5 half-lives), or others (UV or SC Ig, immunoadsorption, plasmapheresis within 4 weeks; IPP-201101 within 3 months).

10a. Study participant had been treated with any biological agent other than those listed above in the past 3 months or within 5 half-lives prior to Visit 2, whichever was longer.

11. Study participant had prior treatment with rituximab in the 6 months prior to Visit 2 or had prior treatment with rituximab in the 12 months prior to Visit 2 and B cell monitoring had shown they did not return to the normal range.

12a. Study participant had a thymectomy in the past 6 months or a thymoma at any time that required chemotherapy and/or radiotherapy prior to Visit 1.

13b. Study participant had any of the following active GI disorders: inflammatory bowel disease, GI ulceration, or diverticulitis.

14. Study participant had participated in another study of an IMP and/or an investigational device within the previous 3 months or was currently participating in another study of an IMP and/or an investigational device.

15a. Study participant had been previously randomised in the current study. Note that rescreening for screen failed participants was allowed with prior consultation and permission of the Medical Monitor.

16. Study participant had experienced a hypersensitivity reaction after exposure to other anti-FcRn drugs.

17a. Study participant with severe (defined as Grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or who had myasthenic crisis or impending crisis at Visits 1 or 2.

18. Study participant had a serum total IgG level ≤5.5g/L.

19. Study participant had absolute neutrophil count <1500 cells/mm3.

20. Study participant had any laboratory abnormality that, in the opinion of the Investigator, was clinically significant, had not resolved by the time of randomisation, and could have jeopardised or compromised the study participant's ability to participate in this study.

21. Study participant had 12-lead ECG with findings considered to be clinically significant upon medical review. The clinical significance of the findings was to be assessed by the Investigator to determine eligibility, and any queries regarding continuation of the study participants were to be addressed with the Medical Monitor.

22b. Study participant had renal impairment, defined as GFR <45ml/min/1.73m2 at Visit 1.

23a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) were >3×upper limit of normal (ULN), or bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN was acceptable if bilirubin was fractionated and direct bilirubin <35%).

Study participant had elevations in total bilirubin (TBL) that were >ULN and <1.5×ULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For randomised study participants with a baseline result >ULN for ALT, AST, ALP, or TBL but <1.5×ULN, a Baseline diagnosis and/or the cause of any clinically meaningful elevation was to be understood and recorded in the eCRF.

If the study participant had >ULN, ALT, AST, or ALP that did not meet the exclusion criterion at Visit 1, the tests were to be repeated, if possible, prior to administration of study treatment to ensure there was no further ongoing clinically relevant increase in these parameters. In the case of a clinically relevant increase, inclusion of the study participant was to be discussed with the medical monitor.

Tests that resulted in ALT, AST, or ALP up to 25% above the exclusion limit (>3×ULN) were to be repeated once for confirmation. This included rescreening.

24. Presence of Hepatitis B surface antigen at Visit 1.

25. Positive Hepatitis C virus (HCV) antibody test result at Visit 1 or within 3 months prior to starting study treatment. Note that study participants with a positive HCV antibody due to prior resolved disease could have been enrolled only if a confirmatory negative HCV ribonucleic acid (RNA) test was obtained.

26. Positive Hepatitis C RNA test result at Visit 1 or within 3 months prior to first dose of study treatment. Note that this test was optional and a study participant with a negative Hepatitis C antibody test was not required to also undergo Hepatitis C RNA testing.

27b. Current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. Note that this was defined except for stable hepatobiliary conditions including Gilbert's syndrome and asymptomatic gallstones.

28. Study participant tested positive for human immunodeficiency virus.

29a. Study participant had a current or medical history of primary immunodeficiency.

30a. Study participant had 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 had been definitively treated with standard of care approaches).

31a. Study participant had a planned elective surgical procedure within 4 months after Visit 1.

32. Study participant had a history of a solid organ transplant or haematopoietic stem cell/marrow transplant.

33. Study participant had corrected QTcF >450 msec (for male participants), or QTc >470 msec (for female participants), or QTc >480 msec in participants with bundle branch block.

34. The study participant was not considered capable of adhering to the protocol visit schedule, or medication intake, according to the judgment of the Investigator.

35. A female study participant, who tested positive for pregnancy, planned to get pregnant during the participation in the study, or who was breastfeeding.

36. Study participant had a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or had suicidal ideation in the past 6 months as indicated by a positive response (yes) to either Questions 4 or 5 of the Columbia Suicide Severity Rating Scale.

37. Criterion removed.

38. Participant with current or medical history of IgA deficiency.

39a. Participant with a medical history of splenectomy.

- **Treatment**

Study participants received a total of 6 SC infusions administered at 1-week intervals during the 6-week treatment period.

Rozanolixizumab was administered as fixed unit doses stratified on body weight tiers (see Table 26)

- treatment group 1 received a dose equivalent to ≈7mg/kg of rozanolixizumab.

- treatment group 2 received a dose equivalent to ≈10mg/kg of rozanolixizumab.

Rozanolixizumab solution for infusion was supplied in a 6mL glass vial, containing no less than 4.0mL extractable volume of rozanolixizumab at a concentration of 140mg/mL. Doses of ≈7mg/kg and ≈10mg/kg were administered as SC abdominal infusion.

The placebo group received 0.9% sodium chloride aqueous solution (physiological saline, preservative free) supplied by a commercial source. A total of 6 SC doses were administered at 1-week intervals in the abdomen.

Table 26: MG0003 dose groups

	Rozanolixizumab sc dose administered (mg)	
Bodyweight	**Treatment group 1 (≈7mg/kg)**	**Treatment group 2 (≈10mg/kg)**
<50kg	280	420
≥50kg to <70kg	420	560
≥70kg to <100kg	560	840
≥100kg	840	1120

≈=equivalent dose; sc=subcutaneous

Justification of treatment duration and follow up period:

The duration of the treatment and observation periods were defined based on data from the previously conducted studies UP0018 and MG0002 (see description of the studies in the tabular overview of clinical studies).

Dose-dependent decreases in total IgG serum concentrations were observed across the studies in healthy participants (UP0018) and patients with gMG (MG0002). In general, the nadir in total IgG serum concentrations occurred within the first 10 days following single doses of rozanolixizumab. After multiple SC administration of rozanolixizumab in MG0002 the maximum decrease in IgG concentrations was achieved after 6 infusions (Day 50), as well as the greatest reductions from Baseline in QMG, MG Composite (MG-C), and MG-ADL. Therefore, a treatment duration of 6 weeks was selected for MG0003 to ensure the maximum treatment effect of rozanolixizumab was captured. Following the last dose administration in UP0018 and MG0002, IgG concentrations recovered toward Baseline levels within approximately 8 weeks. Therefore, an 8-week observation period was defined to follow the recovery of IgG and AChR and MuSK antibodies, as well as monitoring the sustainability of the clinical effects after treatment discontinuation.

Medical devices:

The study sites were supplied with the Crono S-PID pump (manufactured by Cané S.R.L, Torino, Italy) and the Cleo 90 infusion set (manufactured by Smith's Medical ASD Inc, St Paul, MN, USA) for the SC infusion.

Both the Crono S-PID pump and the Cleo 90 infusion set used for the purpose of SC infusions were regarded in Japan as investigational devices, that required adherence to specific reporting obligations (Japan Protocol Section 8.3.9).

Additional medical devices used included the Freedom EDGE and B Braun pumps in Canada.

- **Objectives**

The primary objective was to demonstrate the clinical efficacy of rozanolixizumab in patients with gMG.

The secondary objective was to assess safety and tolerability of rozanolixizumab in gMG patients.

"Other" objectives of this study were:

• To assess PK characteristics of rozanolixizumab.

• To assess the PD effects of rozanolixizumab on IgG, disease-specific autoantibodies.

• To evaluate the emergence and incidence of ADA and impact on PK and PD (added in Protocol Amendment 3, 29 Jul 2020)

• To evaluate the effects of rozanolixizumab on the concentration of total protein, IgM, IgA, and IgE, serum and plasma complement levels, and serum cytokines (added in Protocol Amendment 3, 29 Jul 2020).

• To assess the effect of rozanolixizumab on tetanus IgG antibodies (added in Protocol Amendment 1, 30 Oct 2019).

• To assess the effect of rozanolixizumab on exploratory biomarkers and protein expression and explore the relationship between protein and metabolite biomarkers and cause, progression, and appropriate treatment of gMG (note: results for this exploratory objective are not summarised in this CSR).

- **Outcomes/endpoints**

The **primary efficacy endpoint** was the change from baseline to day 43 (visit 10) in MG-ADL score.

The **secondary efficacy endpoints** were:

- Change from Baseline to Day 43 (Visit 10) in the MG-C score.
- Change from Baseline to Day 43 (Visit 10) in QMG score.
- Change from Baseline to Day 43 (Visit 10) in MG Symptoms Patient-Reported Outcomes (PRO) "Muscle Weakness Fatigability" score.
- Change from Baseline to Day 43 (Visit 10) in MG Symptoms PRO "Physical Fatigue" score.
- Change from Baseline to Day 43 (Visit 10) in MG Symptoms PRO "Bulbar Muscle Weakness" score.
- MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10).

The **"other" efficacy endpoints** were:

- Use of rescue therapy (IVIg or PEX) due to worsening of gMG symptoms for the treatment period and observation period.
- Time to first rescue therapy.
- Time to MG-ADL response.
- MG-ADL, MG-C (defined as ≥3.0 points improvement from Baseline), and QMG responders (defined as ≥3.0 points improvement from baseline) during treatment and observation periods.
- Minimal symptom expression during treatment and observation periods.
- Change from Baseline at each scheduled assessment during the treatment period and observation period in MG-ADL, MG-C, and QMG scores (including and excluding ocular items for all 3), and in MG Symptoms PRO "Muscle Weakness Fatigability", "Physical Fatigue", "Bulbar Muscle Weakness", "Respiratory Muscle Weakness", and "Ocular Muscle Weakness" scores.
- Change from Baseline in Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) during the Treatment Period and Observation Period.
- Change from Baseline to Day 43 (Visit 10) in the MG-QoL15r and in the 5-level Euro Quality of Life 5 Dimension (EQ-5D-5) to Day 43 (Visit 10)
- Change from Baseline in Myasthenia Gravis Impairment Index (MGII) scores during the Treatment Period

All other efficacy variables were summarised descriptively.

- **Sample size**

Expected sample sizes were determined from a simulation study. There were 200 study participants enrolled into the lead-in study MG0003. All eligible study participants from MG0003 were invited to participate in MG0004 until study site approval of MG0007 as well as fulfilment of regulatory requirements.

- **Randomisation and Blinding (masking)**

Randomisation into treatment groups was 1:1:1 and was stratified by MG-specific autoantibody (AChR+ or MuSK+).

Study site pharmacists or other suitably qualified study site personnel who were responsible for preparation of IMP treatments had access to treatment allocations for individual study participants via the IRT. The unblinded pharmacy monitors from the Contract Research Organisation (CRO), and the Clinical Supply Manager also had access to the treatment allocations and to the drug accountability records, if applicable. The following individuals may have had access, as necessary, to the randomisation code as indicated:

• Sponsor patient safety staff, as needed, for reporting serious adverse events (SAEs) to regulatory authorities.

• Members of the Independent Data Monitoring Committee (IDMC) who participated in unblinded sessions were given information about the IMP allocation for those study participants for whom data were provided at these sessions.

• The CRO staff supporting preparation of the data outputs for the IDMC review and/or any interim analyses.

• The independent Medical Monitor external to the Sponsor for monitoring unblinded clinical laboratory data, such as total IgG levels.

If IgG levels dropped below 1g/L, the IMP was temporarily discontinued. If IgG levels were ≥1 and <2g/L, and study participant experienced a nonserious infection which was persistent or recurrent, rozanolixizumab treatment may have temporarily been discontinued.

Temporary treatment discontinuation due to low IgG levels could have been a trigger to unblind the treatment assignment of the specific study to both the study participant and study site personnel. Therefore, infusions continued but were given as mock infusions with only placebo irrespective of prior IMP designation. Allocation of mock kit numbers were handled via the IRT.

An unblinded Medical Monitor informed the Investigator of the initiation of mock infusions and brought attention to any potential infection risk. The Medical Monitor continued to review available safety information for these study participants (e.g, AEs for infection and white cell count) while the IgG levels were at the protocol-defined low threshold values, and directly contacted the Investigator should this review have identified additional information that may have been important in the care of the study participants. When the IgG levels returned to the protocol-defined levels to re-initiate IMP, the unblinded Medical Monitor informed the Investigator of this decision. Based on the clinical situation, the Investigator had the option of holding the dose of IMP until deemed appropriate.

In the event of an emergency, it was possible to determine to which treatment group and dose the study participant has been allocated by contacting the IRT. All study sites were provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent was to be consulted before unblinding, whenever possible. Any unblinding of the study medication performed by the Investigator must have been recorded in the source documents and on the Study Termination eCRF page.

Any inadvertent unblinding was listed as a major protocol deviation.

- **Statistical methods**

Analysis sets

- The Enrolled Set (ES) consisted of all study participants who signed the informed consent form.

- The Randomised Set (RS) consisted of all study participants who were randomised, using the treatment assigned instead of the actual treatment received.

- The Safety Set (SS) consisted of all randomised study participants who received at least 1 dose of IMP, analysed according to the actual treatment the participants received.

- The Pharmacokinetic Per-Protocol Set (PK-PPS) consisted of a subset of the SS, consisting of those study participants who received at least 1 dose of rozanolixizumab, had at least 1 quantifiable concentration of rozanolixizumab post first dose of study treatment, and no important protocol deviations affecting the PK variable, as confirmed during a preanalysis review of the data before database lock. Postbaseline deviations did not necessarily lead to total exclusion of a study participant from the PK-PPS but may have led to exclusion of specific data.

- The Full Analysis Set (FAS) consisted of all study participants in the RS, who had a Baseline and least 1 postbaseline MG-ADL measurement.

Statistical Methods

The MG0003 study was set up using 2 stages, with a formal interim analysis at the end of the first stage (cutoff date 13 Apr 2021, 92 eligible study participants evaluable for the primary endpoint) allowing for early termination for futility of one or both dose groups, or an increase in the planned sample size for Stage 2 if the study continued. Data were reviewed by an IDMC who recommended to continue the study with the 3 treatment arms and without increasing sample size.

The study followed a 2-stage confirmatory group sequential design using a combination test based on the inverse-normal method of combining independent stagewise p-values applying equal weighting of each stage. The primary analysis of the primary efficacy endpoint was based on the RS using a hypothetical & treatment policy strategy for intercurrent events with missing MG-ADL scores handled under a 'missing at random' (MAR) assumption. The primary endpoint was analysed by a stage-wise MMRM with treatment group, baseline MG-ADL score, region, stratification factors and treatment group by day (interaction term) as fixed factors and study participant as a random effect. The MMRM included Days 8, 15, 22, 29, 36, and 43. The model utilised an unstructured covariance pattern for the repeated measures. Additional analyses using different strategies for handling intercurrent events (hypothetical, treatment policy, or composite strategy) were applied. The analyses of the secondary endpoints followed the same approach.

To check the assumptions around the estimand in the (primary) analysis of the primary endpoint, the following sensitivity and supplemental analyses were performed:

• A sensitivity analysis using:

– Hypothetical & Treatment Policy Strategy on FAS.

– Hypothetical & Treatment Policy Strategy with a Jump to Reference (J2R) approach on missing data was used to verify the robustness of the MAR approach.

– Hypothetical & Treatment Policy Strategy based on the subgroup of the RS who received all 6 SC doses.

– Hypothetical & Treatment Policy Strategy based on the subgroup of the FAS excluding confirmed COVID-19 cases.

• A supplemental analysis using:

– Composite Strategy to handle the occurrence of an intercurrent event as treatment failures. A trimmed mean approach was implemented to impute missing data.

– Treatment Policy Strategy to allow intercurrent events was included in the treatment paradigm.

Adjustments for covariates

The efficacy analyses were adjusted for the following covariates:

• Baseline MG-ADL score

• Region (North America, Europe, and Asia [excluding Japan], Japan)

• Stratification factors: MG-specific autoantibodies: AChR(+/-) and MuSK(+/-), both as binary variables

Handling of dropouts or missing data

Summaries of demographics and baseline characteristics are based on all participants in the analysis set and include a "Missing" category (corresponding to participants with missing data for the variable being summarised) as the last row in the list of categories being summarised.

Summaries of safety variables (unless otherwise specified): are based only on those participants with observed data for the variable summarised.

All summaries of PK variables are based on the observed values. No imputation was used.

Imputation methods for missing overall scores for the analyses of primary and secondary efficacy endpoints are listed in Table 27. For binary efficacy endpoints (e.g, QMG responder), missing data was imputed using nonresponse imputation. That is, study participants with missing data at the timepoint of interest and all timepoints after use of rescue medication, were treated as non-responders. For ordinal endpoints (EQ-5D-5L, PGI-S, PGI-C), the observed case method was applied. No further imputation was used.

Table 27: Imputation methods for missing overall scores

Efficacy Endpoints	Statistical Analysis Type	Statistical Analysis Methods	Imputation Methods
Primary	Primary	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 1	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 2	MMRM	Imputation: J2R
	Sensitivity 3	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 4	MMRM	Imputation: maximum likelihood estimation
	Supplemental 1	Trimmed Mean using ANCOVA	Imputation: worst score
	Supplemental 2	MMRM	Imputation: maximum likelihood estimation
Secondary (continuous)	Secondary	MMRM	Imputation: maximum likelihood estimation
	Sensitivity	MMRM	Imputation: J2R
	Supplemental	Trimmed Mean using ANCOVA	Imputation: worst score
Secondary (binary)	Secondary	Logistic model	Imputation: NRI

ANCOVA=analysis of covariance; J2R=Jump to reference; MMRM=mixed model for repeated measures; NRI=nonresponse imputation.

Multiple comparisons/multiplicity

The statistical analysis of the primary efficacy and selected secondary efficacy endpoints accounted for multiplicity and controlled the familywise type I error rate at a 2-sided alpha level of 0.05 by using a parallel gatekeeping testing procedure with a truncated Hochberg test for each of the 6 type I error families (corresponding to the primary endpoint and the 5 secondary endpoints).

The hypotheses were mapped into 2 sets so that hypotheses within each set corresponded to the same rozanolixizumab dose.

Serial restrictions were applied so that the endpoints could only be tested for each dose, if all previous endpoints for that dose were significant.

For family 1, (the primary endpoint hypotheses corresponding to the pairwise comparisons of each dose vs. placebo) the Hochberg truncation parameter was set to 0 which was equivalent to using the Bonferroni approach, where the type I error was split equally between dose level rozanolixizumab ≈7mg/kg and ≈10mg/kg, so that each dose level was tested at a 2-sided alpha level of 0.025. Whereas, for families 2-5 the Hochberg truncation parameter was set to 0.2, and for the final family the truncation parameter was 1, so that the standard Hochberg test was used.

Subgroups

The primary and continuous secondary efficacy endpoints were evaluated for subgroups of interest including Age (18 to <65 years, ≥65 years), age (18 to <65, 65 to <85, ≥85 years), sex (male, female), region (North America, Europe, and Asia [excluding Japan], Japan and stratification factors: MG-specific autoantibodies, AChR (+/-) and MuSK (+/-).

The MG-ADL scores and change from baseline were summarised in the 5 subgroups as above and additional subgroups including duration of disease at Baseline (<median, ≥median), MGFA disease class at Baseline, thymectomy at Baseline (yes, no), baseline MG-ADL category (<5, ≥5).

The following subgroups of MG Baseline medications were derived in the analysis datasets and used for *ad-hoc* reporting purposes including baseline oral steroid (yes, no), baseline immunosuppressants other than oral steroid (yes, no) and baseline cholinesterase inhibitor (yes, no).

All subgroup analyses were descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups was carried out. No subgroup analysis was performed for safety variables. Forest plots are provided to summarise subgroup analysis. Subgroup analyses were only performed for subgroups where there were at least 5 study participants in each subgroup level.

To support the goal of a fixed dosing strategy for rozanolixizumab, additional subgroup analyses were performed by administered dose group for each weight subgroup: weight (<50kg, 50 to <70 kg, 70 to <100kg, ≥100kg, total) and administered dose (placebo, rozanolixizumab 280mg, rozanolixizumab 420mg, rozanolixizumab 560mg, rozanolixizumab 840mg, rozanolixizumab 1120mg, rozanolixizumab total).

Interim analyses and data monitoring

An IDMC was formed to monitor the ongoing safety and efficacy of the study. Futility and samples size adjustment were also reviewed and assessed by the IDMC during a formal interim analysis at the end of Stage 1, when 92 enrolled study participants were evaluable for the primary endpoint. Approximately 3 periodic data reviews (in addition to the futility analysis mentioned above) were planned to be performed: the first periodic data review when approximately 15 study participants had completed the 6-week Treatment Period; the second periodic data review when approximately 60 study participants had completed the 6-week Treatment Period (*ad-hoc,* as needed); and a third review was conducted after

approximately 150 to 180 study participants (dependent on the outcome of the interim analysis) had completed the 6-week Treatment Period. The timing of any further data reviews was decided by the IDMC in conjunction with the Sponsor.

Results

- **Participant flow**

Table 28: Disposition and discontinuation reasons (Randomised Set)

Disposition	Placebo N=67 n (%)	RLZ ≈7mg/kg N=66 n (%)	RLZ ≈10mg/kg N=67 n (%)	All participants N=200 n (%)
Started study	67 (100)	66 (100)	67 (100)	200 (100)
Pre COVID-19	6 (9.0)	5 (7.6)	6 (9.0)	17 (8.5)
During COVID-19	61 (91.0)	61 (92.4)	61 (91.0)	183 (91.5)
Completed study	42 (62.7)	43 (65.2)	43 (64.2)	128 (64.0)
Pre COVID-19	3 (4.5)	3 (4.5)	3 (4.5)	9 (4.5)
During COVID-19	39 (58.2)	40 (60.6)	40 (59.7)	119 (59.5)
Permanently discontinued study	25 (37.3)	23 (34.8)	24 (35.8)	72 (36.0)
Primary reason for study discontinuation				
Pre COVID-19	0	0	0	0
During COVID-19	25 (37.3)	23 (34.8)	24 (35.8)	72 (36.0)
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 (0.5)
Other [a]	18 (26.9)	19 (28.8)	18 (26.9)	55 (27.5)
Due to COVID 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)

≈=equivalent dose; COVID-19=coronavirus disease 2019; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab.
a For the 7 additional "other" reasons for study discontinuation see line listing.
Note: Started study is defined as signing informed consent. Completed Study is defined as having completed the Treatment and Observation Period.
Note: The COVID-19 period is based on the start, completed and discontinuation date relative to the pandemic cutoff date (start date: 20 Mar 2020). This study extended from pre COVID-19 to during COVID-19 period. Post COVID-19 period does not apply.
Note: Mandatory withdrawal and rollover to MG0004 or MG0007 referring to participants requiring rescue therapy in the MG0003 Observation Period. Another 13 study participants rolled over to MG0004 (6 study participants) or MG0007 (7) after completion of the Treatment Period and during the Observation Period (data on file); the reasons provided for discontinuation for these study participants are "lack of efficacy" (6 study participants), "worsening of symptoms" (5), "adverse event" (1), and "other" (1).

The median duration of study medication was 36.0 days for all treatment groups (including mock infusions). All study participants received at least 1 infusion (excluding mock infusions). A total of 52 (81.3%) study participants in the rozanolixizumab ≈7mg/kg group, 48 (69.6%) in the ≈10mg/kg group, and 56 (83.6%) in the placebo group received all 6 infusions (excluding mock infusions).

Mock infusions using placebo were given to reduce unblinding potential when IgG levels dropped below 1g/L. The number of infusions received including mock infusions is summarised in Table 29. No study participants in the placebo group needed mock infusions, whereas mock infusions were administered in both rozanolixizumab groups: 3 total infusions in 2 study participants in the ≈7mg/kg group and 4 total

infusions in 2 study participants (2 infusions each) in the ≈10mg/kg group. Study participants required mock infusions on Day 29 and Day 36.

Table 29: Number of infusions received (Safety Set)

	Statistic	Placebo N=67	RLZ ~7mg/kg N=64	RLZ ~10mg/kg N=69	RLZ Total N=133	All Participants N=200
Number of Infusions						
	n	67	64	69	133	200
	Mean	5.7	5.7	5.5	5.6	5.7
	SD	0.6	0.9	1.0	0.9	0.8
	Median	6.0	6.0	6.0	6.0	6.0
	Min	3	1	1	1	1
	Max	6	6	6	6	6
Number of Infusions						
1	n (%)	0	1 (1.6)	1 (1.4)	2 (1.5)	2 (1.0)
2	n (%)	0	1 (1.6)	1 (1.4)	2 (1.5)	2 (1.0)
3	n (%)	1 (1.5)	0	1 (1.4)	1 (0.8)	2 (1.0)
4	n (%)	4 (6.0)	2 (3.1)	5 (7.2)	7 (5.3)	11 (5.5)
5	n (%)	6 (9.0)	6 (9.4)	11 (15.9)	17 (12.8)	23 (11.5)
6	n (%)	56 (83.6)	54 (84.4)	50 (72.5)	104 (78.2)	160 (80.0)

- **Recruitment**

Study period: Approximately 2 years and 3 months

First study participant enrolled: 18 Jun 2019

Last study participant completed: 17 Sep 2021

A total of 200 participants were randomised from 81 sites (North America, Europe, and Asia).

- **Conduct of the study**

There were 6 protocol amendments (2 in Japan) concerning adding extra endpoints (see endpoint section), alignment of inclusion criteria, inclusion of study MG0007 among others.

Overall, 1 (0.5%) study participant had an important protocol deviation (IPD) during the pre-COVID-19 period (incorrect treatment or dose) and 21 (10.5%) had at least 1 IPD during the COVID-19 period (most commonly procedural non-compliance, in 8 [4.0%] study participants).

No study participants were excluded from any analysis sets due to important protocol deviations.

- **Baseline data**

Table 30: Study participant demographics (Randomised Set)

Variable Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67	All Participants N=200
Age (years) [a]				
Mean (SD)	50.4 (17.7)	53.2 (14.7)	51.9 (16.5)	51.8 (16.3)
Median	51.0	52.0	54.0	52.0
Min, max	18, 85	22, 89	19, 81	18, 89
Age category, n (%) [b]				
18 to <65 years	51 (76.1)	49 (74.2)	51 (76.1)	151 (75.5)
65 to <85 years	15 (22.4)	16 (24.2)	16 (23.9)	47 (23.5)
≥85 years	1 (1.5)	1 (1.5)	0	2 (1.0)

Age category, n (%) [c]				
≤18 years	1 (1.5)	0	0	1 (0.5)
19 to <65 years	50 (74.6)	49 (74.2)	51 (76.1)	150 (75.0)
≥65 years	16 (23.9)	17 (25.8)	16 (23.9)	49 (24.5)
Sex, n (%)				
Male	20 (29.9)	27 (40.9)	32 (47.8)	79 (39.5)
Female	47 (70.1)	39 (59.1)	35 (52.2)	121 (60.5)
Weight (kg)				
Mean (SD)	80.80 (22.57)	79.56 (25.52)	83.06 (23.73)	81.15 (23.88)
Median	80.00	78.00	76.60	78.00
Min, max	39.7, 150.5	37.7, 154.2	46.9, 155.6	37.7, 155.6
Height (cm)				
Mean (SD)	168.98 (9.86)	169.00 (9.98)	171.07 (9.70)	169.69 (9.85)
Median	168.00	170.00	170.00	169.75
Min, max	149.0, 193.0	148.9, 193.0	155.0, 198.1	148.9, 198.1
BMI (kg/m^2)				
Mean (SD)	28.03 (6.19)	27.38 (6.86)	28.07 (6.28)	27.83 (6.42)
Median	28.12	26.43	26.98	27.16
Min, max	13.7, 41.7	14.2, 47.6	15.3, 45.5	13.7, 47.6
Body weight category, n (%)				
<50	4 (6.0)	7 (10.6)	1 (1.5)	12 (6.0)
50 to <70	16 (23.9)	19 (28.8)	26 (38.8)	61 (30.5)
70 to <100	35 (52.2)	26 (39.4)	22 (32.8)	83 (41.5)
≥100	12 (17.9)	14 (21.2)	18 (26.9)	44 (22.0)
Racial group, n (%) [d]				
Asian	5 (7.5)	9 (13.6)	7 (10.4)	21 (10.5)
Black	1 (1.5)	0	4 (6.0)	5 (2.5)
Native Hawaiian or other Pacific Islander	1 (1.5)	0	0	1 (0.5)
White	46 (68.7)	41 (62.1)	49 (73.1)	136 (68.0)
Missing	14 (20.9)	16 (24.2)	7 (10.4)	37 (18.5)
Ethnicity, n (%) [d]				
Hispanic or Latino	5 (7.5)	5 (7.6)	3 (4.5)	13 (6.5)
Not Hispanic or Latino	48 (71.6)	47 (71.2)	58 (86.6)	153 (76.5)
Missing	14 (20.9)	14 (21.2)	6 (9.0)	34 (17.0)
Region, n (%)				
North America	21 (31.3)	21 (31.8)	18 (26.9)	60 (30.0)
Europe	41 (61.2)	36 (54.5)	43 (64.2)	120 (60.0)
Asia (excluding Japan)	1 (1.5)	4 (6.1)	2 (3.0)	7 (3.5)
Japan	4 (6.0)	5 (7.6)	4 (6.0)	13 (6.5)

Country, n (%)				
United States	16 (23.9)	11 (16.7)	14 (20.9)	41 (20.5)
Poland	9 (13.4)	10 (15.2)	8 (11.9)	27 (13.5)
Canada	5 (7.5)	10 (15.2)	4 (6.0)	19 (9.5)
France	9 (13.4)	6 (9.1)	3 (4.5)	18 (9.0)
Russian Federation	5 (7.5)	3 (4.5)	6 (9.0)	14 (7.0)
Georgia	4 (6.0)	4 (6.1)	5 (7.5)	13 (6.5)
Italy	4 (6.0)	3 (4.5)	6 (9.0)	13 (6.5)
Japan	4 (6.0)	5 (7.6)	4 (6.0)	13 (6.5)
Germany	5 (7.5)	1 (1.5)	3 (4.5)	9 (4.5)
Spain	1 (1.5)	5 (7.6)	2 (3.0)	8 (4.0)
Taiwan	1 (1.5)	4 (6.1)	2 (3.0)	7 (3.5)
Denmark	1 (1.5)	0	4 (6.0)	5 (2.5)
Czech Republic	0	2 (3.0)	1 (1.5)	3 (1.5)
Hungary	0	0	1 (1.5)	1 (0.5)

≈=equivalent dose; BMI=body mass index; Max=maximum; Min=minimum; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SD=standard deviation Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).
a Missing age was calculated as year of informed consent signed – year of birth.
b EudraCT age categories.
c Clinicaltrials.gov age categories.
d Race and ethnicity are prohibited to collect in France and Canada.

Table 31: Baseline characteristics (Randomised Set)

Variable Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67	All Participants 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 (%)				
Yes	31 (46.3)	32 (48.5)	20 (29.9)	83 (41.5)
No	36 (53.7)	34 (51.5)	47 (70.1)	117 (58.5)
MG-ADL score				
Mean (SD)	8.4 (3.4)	8.4 (3.8)	8.1 (2.9)	8.3 (3.4)
Median	8.0	8.0	8.0	8.0
Min, max	3, 16	3, 18	3, 16	3, 18
MG-ADL group, n (%)				
≥5	57 (85.1)	55 (83.3)	61 (91.0)	173 (86.5)
<5	10 (14.9)	11 (16.7)	6 (9.0)	27 (13.5)

QMG score				
Mean (SD)	15.8 (3.5)	15.4 (3.7)	15.6 (3.7)	15.6 (3.6)
Median	15.0	15.0	15.0	15.0
Min, max	11, 23	9, 27	11, 27	9, 27
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)	9.418 (9.348)	6.877 (6.799)	9.561 (9.895)	8.627 (8.836)
Median	6.790	5.280	5.703	5.799
Min, max	0.14, 48.94	0.14, 33.09	0.25, 46.44	0.14, 48.94
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	38.0	46.0	40.0	44.0
Min, max	12, 79	13, 83	11, 76	11, 83
Historical autoantibody status, n (%) [a]				
AChR+	59 (88.1)	60 (90.9)	60 (89.6)	179 (89.5)
MuSK+	8 (11.9)	5 (7.6)	8 (11.9)	21 (10.5)
Baseline autoantibody status, n (%) [b]				
AChR+	53 (79.1)	56 (84.8)	56 (83.6)	165 (82.5)
MuSK+	8 (11.9)	4 (6.1)	4 (6.0)	16 (8.0)
Total IgG (g/L)				
Mean (SD)	10.20 (2.61)	10.16 (3.18)	9.67 (2.61)	10.01 (2.81)
Median	10.36	9.67	9.27	9.56
Min, max	5.9, 16.5	5.3, 21.3	5.9, 17.0	5.3, 21.3

≈=equivalent dose; AChR=acetylcholine receptor; CRF=case report form; IgG=immunoglobulin G; Max=maximum; MG=Myasthenia Gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; Min=minimum; MuSK=muscle-specific kinase; n=number of study participants; N=total number of study participants in treatment group; QMG=Quantitative Myasthenia Gravis; RLZ=rozanolixizumab; SD=standard deviation Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).

a AChR and MuSK autoantibody status are captured from "Confirmatory (Historical) Diagnostic Tests for Primary Condition" CRF.

b AChR and MuSK autoantibody status are captured from Baseline Visit

Table 32: Past gMG medications (Randomised Set)

Pharmacological subgroup Preferred term	Placebo N=67 n (%)	RLZ ≈7mg/kg N=66 n (%)	RLZ ≈10mg/kg N=67 n (%)	All Participants N=200 n (%)
Corticosteroids for systemic use, plain	**10 (14.9)**	**9 (13.6)**	**18 (26.9)**	**37 (18.5)**
Prednisolone	6 (9.0)	5 (7.6)	6 (9.0)	17 (8.5)
Prednisone	3 (4.5)	2 (3.0)	6 (9.0)	11 (5.5)
Methylprednisolone sodium succinate	3 (4.5)	3 (4.5)	4 (6.0)	10 (5.0)
Methylprednisolone	0	0	3 (4.5)	3 (1.5)
Cortisone	0	1 (1.5)	0	1 (0.5)
Immunosuppressants	**8 (11.9)**	**9 (13.6)**	**7 (10.4)**	**24 (12.0)**
Azathioprine	4 (6.0)	5 (7.6)	4 (6.0)	13 (6.5)
Ciclosporin	0	1 (1.5)	2 (3.0)	3 (1.5)
Eculizumab	1 (1.5)	1 (1.5)	1 (1.5)	3 (1.5)
Mycophenolate mofetil	2 (3.0)	1 (1.5)	1 (1.5)	4 (2.0)
Tacrolimus	0	1 (1.5)	0	1 (0.5)
Tacrolimus monohydrate	1 (1.5)	0	0	1 (0.5)
Parasympathomimetics	**7 (10.4)**	**6 (9.1)**	**5 (7.5)**	**18 (9.0)**
Pyridostigmine bromide	5 (7.5)	5 (7.6)	1 (1.5)	11 (5.5)
Pyridostigmine	1 (1.5)	1 (1.5)	4 (6.0)	6 (3.0)
Neostigmine metilsulfate	1 (1.5)	0	0	1 (0.5)

≈=equivalent dose; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab Note: Past medications include any medications that started and stopped before the first administration of IMP.

Table 33: Baseline gMG medications (Randomised Set)

Pharmacological Subgroup Preferred Term	Placebo N=67 n (%)	RLZ ≈7mg/kg N=66 n (%)	RLZ ≈10mg/kg N=67 n (%)	All Participants N=200 n (%)
Corticosteroids for Systemic Use, Plain	**38 (56.7)**	**43 (65.2)**	**48 (71.6)**	**129 (64.5)**
Prednisone	19 (28.4)	28 (42.4)	25 (37.3)	72 (36.0)
Prednisolone	13 (19.4)	11 (16.7)	16 (23.9)	40 (20.0)
Methylprednisolone	4 (6.0)	4 (6.1)	7 (10.4)	15 (7.5)
Deflazacort	2 (3.0)	0	0	2 (1.0)
Immunosuppressants	**33 (49.3)**	**32 (48.5)**	**38 (56.7)**	**103 (51.5)**
Azathioprine	19 (28.4)	17 (25.8)	20 (29.9)	56 (28.0)
Mycophenolate mofetil	7 (10.4)	8 (12.1)	5 (7.5)	20 (10.0)
Tacrolimus	4 (6.0)	4 (6.1)	6 (9.0)	14 (7.0)
Ciclosporin	3 (4.5)	2 (3.0)	4 (6.0)	9 (4.5)
Methotrexate	0	0	2 (3.0)	2 (1.0)
Mycophenolic acid	0	1 (1.5)	1 (1.5)	2 (1.0)
Leflunomide	0	1 (1.5)	0	1 (0.5)

Parasympathomimetics	**60 (89.6)**	**55 (83.3)**	**57 (85.1)**	**172 (86.0)**
Pyridostigmine bromide	43 (64.2)	39 (59.1)	41 (61.2)	123 (61.5)
Pyridostigmine	14 (20.9)	13 (19.7)	15 (22.4)	42 (21.0)
Ambenonium chloride	4 (6.0)	2 (3.0)	1 (1.5)	7 (3.5)
Ambenonium	0	2 (3.0)	0	2 (1.0)
Distigmine	0	1 (1.5)	0	1 (0.5)
Distigmine bromide	1 (1.5)	0	0	1 (0.5)

≈=equivalent dose; gMG=generalised myasthenia gravis; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab Note: Baseline medications include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).

- **Numbers analysed**

All study participants were analysed as randomised except for 2 study participants in the rozanolixizumab ≈7mg/kg group, who had important protocol deviations of incorrect treatment dose and received rozanolixizumab ≈10mg/kg at the Baseline Visit. These 2 study participants were analysed as part of the rozanolixizumab ≈10mg/kg group for the SS and PK-PPS.

Efficacy analyses were performed primarily on the RS, unless otherwise specified. Safety and immunological analyses were performed on the SS. Pharmacokinetic analyses were performed on the PK-PPS and PD analyses were performed on the SS.

Table 34: Disposition of analysis sets (Randomised Set)

Analysis Set	Placebo N=67 n (%)	RLZ ≈7mg/kg N=66 n (%)	RLZ ≈10mg/kg N=67 n (%)	All Participants N=200 n (%)
RS	67 (100)	66 (100)	67 (100)	200 (100)
SS	67 (100)	64 (97.0)	69 (103.0)	200 (100)
FAS	67 (100)	66 (100)	67 (100)	200 (100)
PK-PPS	0	64 (97.0)	69 (103.0)	133 (66.5)

≈=equivalent dose; FAS=full analysis set; n=number of study participants; N=total number of study participants in treatment group; PK-PPS=pharmacokinetic per-protocol set; RLZ=rozanolixizumab; RS=randomised set; SS=safety set Note: As per unblinded protocol deviation report, 2 study participants were randomised to RLZ ≈7mg/kg, but were administrated RLZ ≈10mg/kg at the Baseline Visit. These 2 study participants were analysed as part of the RLZ ≈7mg/kg group in RS and FAS, but in RLZ ≈10mg/kg group in SS and PK-PPS.

- **Outcomes and estimation**

Primary endpoint – MG-ADL change

Table 35: MG-ADL change from Baseline to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, Randomised Set)

Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67
n	62	65	65
Mean (SE)	-0.65 (0.363)	-3.22 (0.480)	-3.20 (0.403)
Median	-1.0	-3.0	-3.0
Min, max	-6.0, 9.0	-13.0, 7.0	-10.0, 7.0
LS Mean (SE)	-0.784 (0.488)	-3.370 (0.486)	-3.403 (0.494)
Difference vs Placebo [a]	-	-2.586	-2.619
95% CI for difference [b]	-	-4.091, -1.249	-3.994, -1.163
p-value for difference [b]	-	<0.001	<0.001

≈=equivalent dose; COVID-19=coronavirus disease 2019; CI=confidence interval; ICE=intercurrent event; IMP=investigational medicinal product; LS=Least Square; MAR=missing at random; Max=maximum; MG-ADL=Myasthenia Gravis Activities of Daily Living; Min=minimum; MMRM=mixed model repeated measure; n=number of study participants with data at Day 43; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SE=standard error; TEAE=treatment-emergent adverse event
Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).
Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability.
Note: The analysis is based on the Hypothetical & Treatment Policy Strategy, where study participants who experience ICEs regarding use of rescue therapy were treated as missing at and after the point of the ICE for the purpose of analysis. Data from study participants who discontinued treatment or the study due to TEAEs or COVID-19 infection or non-COVID-19 infection-related issues before Day 43 were used regardless of whether ICEs occurred. Any missing MG-ADL scores (including missing data after the ICEs) were handled based on maximum likelihood estimation under MAR assumption.
Note: Baseline is defined as the last available value before or on the same date (and same time if time is collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
a The differences presented is RLZ (≈7mg/kg or ≈10mg/kg) minus placebo.
b All outputs are from the combined MMRM, except CIs and p-values, which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

A number of sensitivity and supplemental analyses were done for the primary hypothesis (see statistical method subsection). All sensitivity and supplemental analyses supported the primary analysis.

Secondary endpoints

- Change from Baseline to Day 43 (Visit 10) in the MG-Composite (MG-C) score.

Table 36: MG-C change from Baseline to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, Randomised Set)

Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67
n	62	65	62
Mean (SE)	-1.47 (0.722)	-5.23 (0.828)	-7.13 (0.857)
Median	-2.0	-4.0	-6.0
Min, max	-15.0, 11.0	-19.0, 10.0	-27.0, 6.0
LS Mean (SE)	-2.029 (0.917)	-5.930 (0.916)	-7.554 (0.934)
Difference vs Placebo [a]	-	-3.901	-5.525
95% CI for difference [b]	-	-6.634, -1.245	-8.303, -2.968
p-value for difference [b]	-	<0.001	<0.001

≈=equivalent dose; CI=Confidence Interval; COVID-19=coronavirus disease 2019; ICE=intercurrent event; IMP=investigational medicinal product; LS=Least Square; MAR=missing at random; Max=maximum; MG-C=Myasthenia Gravis Composite score; Min=minimum; MMRM=mixed model repeated measure; n=number of study participants with data at Day 43; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SE=standard error; TEAE=treatment-emergent adverse event
Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).
Note: MG Composite scores range from 0 to 50, with a higher score indicating more severe disease.
Note: The analysis was based on the Hypothetical & Treatment Policy Strategy, where study participants who experienced ICEs regarding use of rescue therapy were treated as missing at and after the point of the ICE for the purpose of analysis. Data from study participants who discontinued treatment or the study due to TEAEs or COVID-19 infection or non-COVID-19 infection-related issues before Day 43 were used regardless of whether ICEs occurred. Any missing MG-C scores (including missing data after the intercurrent events) were handled based on maximum likelihood estimation under MAR assumption. Note: Baseline was defined as the last available value before or on the same date (and same time if time is collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
a The difference presented is RLZ (≈7mg/kg or ≈10mg/kg) minus placebo.
b All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

- Change from Baseline to Day 43 (Visit 10) in QMG score

Table 37: QMG change from Baseline to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, Randomised Set)

Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67
n	62	65	62
Mean (SE)	-0.89 (0.525)	-4.22 (0.574)	-5.62 (0.655)
Median	-0.5	-4.0	-5.0
Min, max	-10.0, 11.0	-13.0, 4.0	-17.0, 5.0
LS Mean (SE)	-1.915 (0.682)	-5.398 (0.679)	-6.672 (0.692)
Difference vs Placebo [a]	-	-3.483	-4.756
95% CI for difference [b]	-	-5.614, -1.584	-6.821, -2.859
p-value for difference [b]	-	<0.001	<0.001

≈=equivalent dose; CI=Confidence Interval; COVID-19=coronavirus disease 2019; ICE=intercurrent event; IMP=investigational medicinal product; LS=Least Square; MAR=missing at random; Max=maximum; Min=minimum; MMRM=mixed model repeated measure; n=number of study participants with data at Day 43; N=total number of study participants in treatment group; QMG=Quantitative Myasthenia Gravis score; RLZ=rozanolixizumab; SE=standard error; TEAE=treatment-emergent adverse event
Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).
Note: The total QMG score ranges from 0 to 39 with a higher score indicating more severe disability.

Note: The analysis was based on the Hypothetical & Treatment Policy Strategy, where participants who experienced ICEs regarding use of rescue therapy were treated as missing at and after the point of the ICE for the purpose of analysis. Data from study participants who discontinued treatment or the study due to TEAEs or COVID-19 infection or non-COVID-19 infection-related issues before Day 43 were used regardless of whether ICEs occurred. Any missing QMG scores (including missing data after the ICE) was handled based on maximum likelihood estimation under MAR assumption. Note: Baseline was defined as last available value before or on the same date (and same time if time is collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
a The difference presented is RLZ (≈7mg/kg or ≈10mg/kg) minus placebo.
b All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

- Change from Baseline to Day 43 (Visit 10) in MG Symptoms Patient-Reported Outcomes (PRO) "Muscle Weakness Fatigability", "Physical Fatigue", "Bulbar Muscle Weakness" scores.

Table 38: Change from Baseline to Day 43 in the primary and the secondary efficacy endpoints included in the sequential hierarchical procedure (Hypothetical and Treatment Policy Strategy, RS)

Statistic	Placebo N=67	RLZ≈7mg/kg; N=66	RLZ≈10mg/kg; N=67	Placebo N=67	RLZ≈7mg/kg; N=66	RLZ≈10mg/kg; N=67	Placebo N=67	RLZ≈7mg/kg; N=66	RLZ≈10mg/kg; N=67
	MG-ADL (primary endpoint)			MG-C			QMG		
LS Mean (SE)	-0.784 (0.488)	-3.370 (0.486)	-3.403 (0.494)	-2.029 (0.917)	-5.930 (0.916)	-7.554 (0.934)	-1.915 (0.682)	-5.398 (0.679)	-6.672 (0.692)
Difference[a] vs placebo		-2.586	-2.619	-	-3.901	-5.525	-	-3.483	-4.756
95% CI for difference[b]		-4.091, -1.249	-3.994, -1.163	-	-6.634, -1.245	-8.303, -2.968	-	-5.614, -1.584	-6.821, -2.859
p-value for difference[b]		<0.001	<0.001	-	<0.001	<0.001	-	<0.001	<0.001
MG Symptoms PRO	**Muscle Weakness Fatigability**			**Physical Fatigue**			**Bulbar Muscle Weakness**		
LS Mean (SE)	-10.588 (3.034)	-23.029 (3.034)	-25.751 (3.095)	-10.637 (3.051)	-19.287 (3.046)	-25.459 (3.107)	-3.519 (2.397)	-14.839 (2.406)	-14.224 (2.464)
Difference[a] vs placebo	-	-12.441	-15.163	-	-8.650	-14.822	-	-11.320	-10.705
95% CI for difference[b]	-	-21.804, -4.089	-23.596, -6.450	-	-18.058, -0.134	-23.759, -5.936	-	-18.958, -4.998	-17.787, -3.998
p-value for difference[b]	-	<0.001	<0.001	-	0.012	<0.001	-	<0.001	<0.001

≈=approximate dose; CI=confidence interval; COVID-19=coronavirus disease 2019; ICE=intercurrent event; IMP=investigational medicinal product; LS=least square; MAR=missing at random; MG-ADL=myasthenia gravis Activities of Daily Living; MG-C=Myasthenia Gravis Composite; MMRM=mixed model repeated measure; n=number of study participants with data at Day 43; N=total number of study participants in treatment group; PRO=patient-reported outcome; QMG=quantitative myasthenia gravis; RLZ=rozanolixizumab; RS=randomised set; SE=standard error; TEAE=treatment-emergent adverse event
Notes: An order of formal hypotheses testing for the primary and key secondary endpoints was defined: change from Baseline to Day 43 in 1) MG-ADL score, 2) MG-C score, 3) QMG score, 4) MG Symptoms PRO Muscle Weakness Fatigability score, 5) MG Symptoms PRO Physical Fatigue score, 6) MG Symptoms PRO Bulbar Muscle Weakness score.
The analysis is based on the Hypothetical & Treatment Policy strategy, where study participants who experience ICEs regarding use of rescue therapy were treated as missing at and after the point of the ICE for the purpose of analysis. Data from study participants who discontinued treatment or the study due to TEAEs or COVID-19 infection or nonCOVID-19 infection-related issues prior to Day 43 were used regardless of whether ICEs occurred. Any missing scores (including missing data after the ICEs) were handled based on maximum likelihood estimation under MAR assumption. Baseline is defined as the last available value prior to or on the same date (and same time if time is collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
a The differences presented are RLZ (7mg/kg or 10mg/kg) minus placebo.
b All outputs are from the combined MMRM, except CIs and p-values, which are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method

- MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)

Table 39:MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10) (Composite Strategy, Randomised Set)

Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67
n	67	66	67
Responder, n (%)	19 (28.4)	45 (68.2)	41 (61.2)
Nonresponder, n (%)	48 (71.6)	21 (31.8)	26 (38.8)
Odds Ratio vs Placebo [a]	-	5.765	4.273
95% CI for Odds Ratio [b]	-	2.100, 14.882	1.653, 11.791
Wald p-value [b]	-	<0.001	<0.001

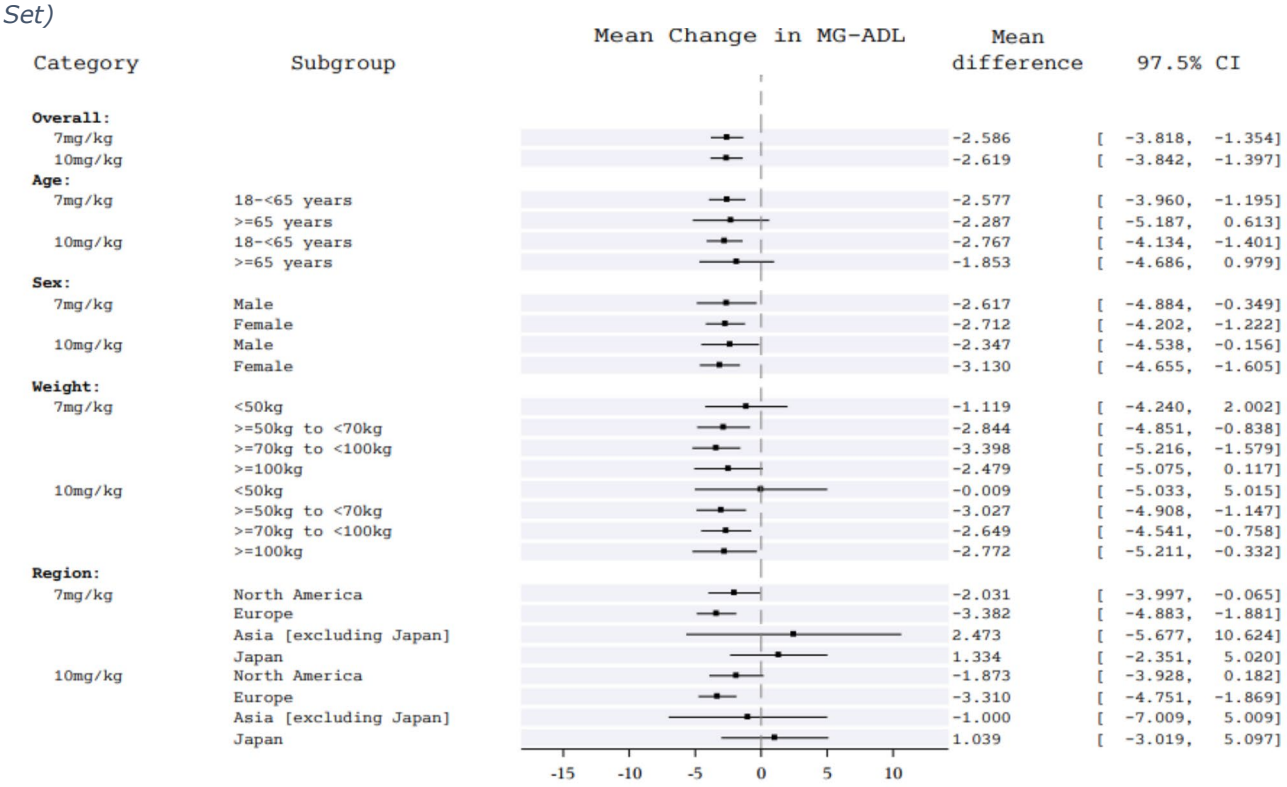
≈=equivalent dose; AChR=acetylcholine receptor; CI=confidence interval; IMP=investigational medicinal product; MG-ADL=Myasthenia Gravis Activities of Daily Living; MuSK=muscle-specific kinase; n=number of study participants with data at Day 43; N=total number of study participants in treatment group; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event
Note: Combined data are shown (ie, from all study participants, including Stage 1 and Stage 2).
Note: Participants were classified as MG-ADL responders if the value was ≥2-point improvement (decrease) from Baseline. Note: The analysis was based on the Composite Strategy, where study participants who received rescue therapy before Day 43 or discontinued from treatment or from the study due to TEAEs were treated as non-responders. Any missing data due to other reasons was imputed as non-responders.
Note: Baseline was defined as last available value before or on the same date (and same time if time was collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
Note: Percentages are based on the number of participants with data at Day 43 in the Randomised Set.
a The odds ratios of the responder rates at Day 43 are estimated and tested between treatment groups (each RLZ dose vs placebo) using logistic regression model with factors of treatment group, Baseline MG-ADL score, and stratification factor (AChR+ or MuSK+). An odds ratio >1 indicates a greater likelihood of response on RLZ compared with placebo.
b All outputs are from the combined model, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method. The reported p-value is unadjusted for multiple testing.

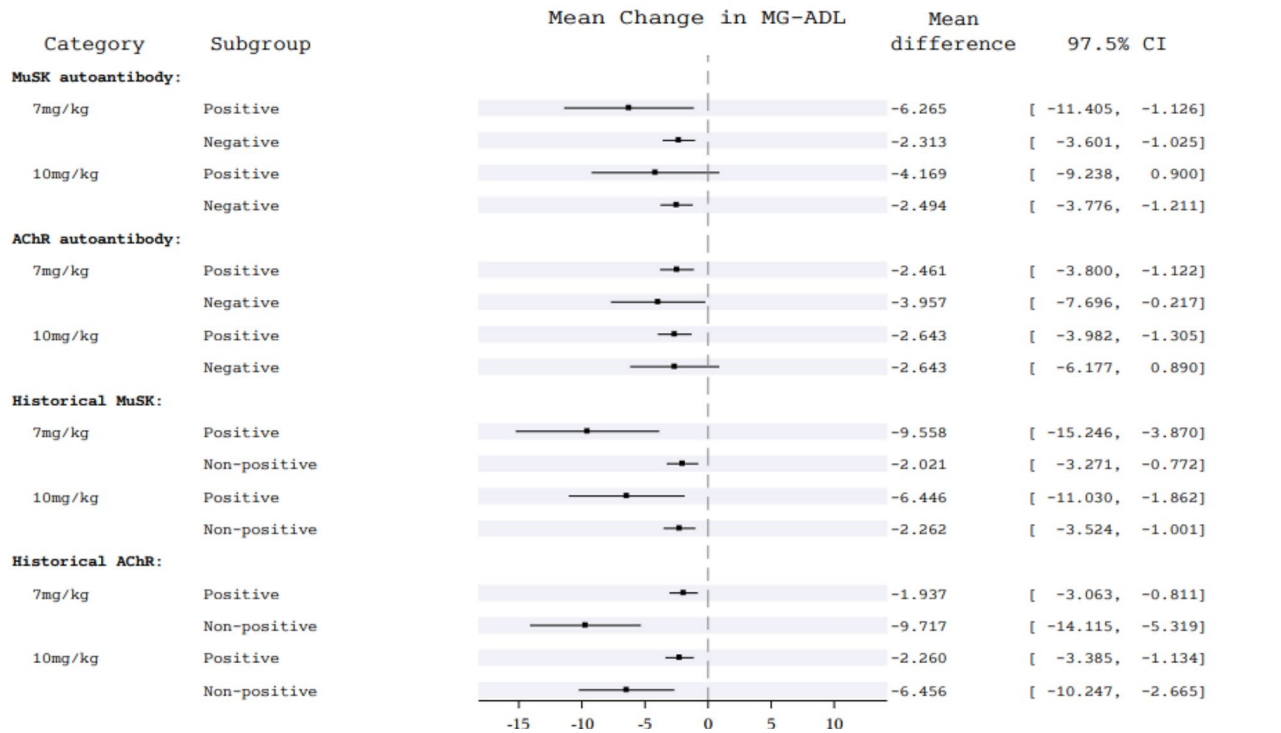
- **Ancillary analyses**

Subgroup analyses of the primary efficacy endpoint

Changes from Baseline in MG-ADL total score to Day 43 were generally consistent with the results in the overall study population for all subgroups except the following ones, all with a low number of study participants available for the analysis: Japanese study participants (5 study participants in the rozanolixizumab ≈7mg/kg group, 4 in the ≈10mg/kg group, and 4 in the placebo group), Asian (excluding Japanese) study participants (4, 2, and 1), and study participants with body weight <50kg (7, 1, and 4).

Figure 19: Forest plot of MG-ADL change from Baseline to Day 43 (Visit 10) by subgroups (Randomised Set)





AChR=acetylcholine receptor; CI=confidence interval; MG-ADL=Myasthenia Gravis Activities of Daily Living; MuSK=muscle-specific kinase
Note: A change to the left favors rozanolixizumab.

Table 40: MG-ADL Responder Rates (Observed) by MG-specific Autoantibody MuSK + (Randomised set)

Period/ Visit Statistic	Placebo N=8	RLZ ~7mg/kg N=4	RLZ ~10mg/kg N=4	RLZ Total N=8
Treatment/ Day 8				
n	8	4	4	8
Responder n (%)	2 (25.0)	2 (50.0)	1 (25.0)	3 (37.5)
Non-responder n (%)	6 (75.0)	2 (50.0)	3 (75.0)	5 (62.5)
Treatment/ Day 15				
n	8	4	4	8
Responder n (%)	1 (12.5)	3 (75.0)	2 (50.0)	5 (62.5)
Non-responder n (%)	7 (87.5)	1 (25.0)	2 (50.0)	3 (37.5)
Treatment/ Day 22				
n	8	4	3	7
Responder n (%)	1 (12.5)	4 (100)	1 (33.3)	5 (71.4)
Non-responder n (%)	7 (87.5)	0	2 (66.7)	2 (28.6)
Treatment/ Day 29				
n	8	4	3	7
Responder n (%)	3 (37.5)	4 (100)	2 (66.7)	6 (85.7)
Non-responder n (%)	5 (62.5)	0	1 (33.3)	1 (14.3)
Treatment/ Day 36				
n	7	4	3	7
Responder n (%)	2 (28.6)	4 (100)	3 (100)	7 (100)
Non-responder n (%)	5 (71.4)	0	0	0
Treatment/ Day 43				
n	7	4	3	7
Responder n (%)	1 (14.3)	4 (100)	3 (100)	7 (100)
Non-responder n (%)	6 (85.7)	0	0	0
Observation/ Day 57				
n	7	3	4	7
Responder n (%)	3 (42.9)	3 (100)	4 (100)	7 (100)
Non-responder n (%)	4 (57.1)	0	0	0
Observation/ Day 71				
n	7	3	3	6
Responder n (%)	4 (57.1)	3 (100)	1 (33.3)	4 (66.7)
Non-responder n (%)	3 (42.9)	0	2 (66.7)	2 (33.3)
Observation/ Day 85				
n	6	2	3	5
Responder n (%)	2 (33.3)	2 (100)	1 (33.3)	3 (60.0)
Non-responder n (%)	4 (66.7)	0	2 (66.7)	2 (40.0)
Observation/ Day 99				
n	7	4	4	8
Responder n (%)	2 (28.6)	1 (25.0)	2 (50.0)	3 (37.5)
Non-responder n (%)	5 (71.4)	3 (75.0)	2 (50.0)	5 (62.5)

Table 41: MG-ADL Responder Rates (Observed) by MG-specific Autoantibody AChR + (Randomised set)

Period/ Visit Statistic	Placebo N=55	RLZ ~7mg/kg N=60	RLZ ~10mg/kg N=60	RLZ Total N=120
Treatment/ Day 8				
n	54	60	59	119
Responder n (%)	14 (25.9)	21 (35.0)	23 (39.0)	44 (37.0)
Non-responder n (%)	40 (74.1)	39 (65.0)	36 (61.0)	75 (63.0)
Treatment/ Day 15				
n	53	56	57	113
Responder n (%)	13 (24.5)	27 (48.2)	27 (47.4)	54 (47.8)
Non-responder n (%)	40 (75.5)	29 (51.8)	30 (52.6)	59 (52.2)
Treatment/ Day 22				
n	52	56	58	114
Responder n (%)	14 (26.9)	33 (58.9)	32 (55.2)	65 (57.0)
Non-responder n (%)	38 (73.1)	23 (41.1)	26 (44.8)	49 (43.0)
Treatment/ Day 29				
n	51	57	56	113
Responder n (%)	14 (27.5)	38 (66.7)	32 (57.1)	70 (61.9)
Non-responder n (%)	37 (72.5)	19 (33.3)	24 (42.9)	43 (38.1)
Treatment/ Day 36				
n	49	57	54	111
Responder n (%)	17 (34.7)	35 (61.4)	34 (63.0)	69 (62.2)
Non-responder n (%)	32 (65.3)	22 (38.6)	20 (37.0)	42 (37.8)
Treatment/ Day 43				
n	52	58	56	114
Responder n (%)	17 (32.7)	41 (70.7)	38 (67.9)	79 (69.3)
Non-responder n (%)	35 (67.3)	17 (29.3)	18 (32.1)	35 (30.7)
Observation/ Day 57				
n	43	50	56	106
Responder n (%)	17 (39.5)	30 (60.0)	33 (58.9)	63 (59.4)
Non-responder n (%)	26 (60.5)	20 (40.0)	23 (41.1)	43 (40.6)
Observation/ Day 71				
n	38	47	53	100
Responder n (%)	15 (39.5)	26 (55.3)	23 (43.4)	49 (49.0)
Non-responder n (%)	23 (60.5)	21 (44.7)	30 (56.6)	51 (51.0)
Observation/ Day 85				
n	37	39	41	80
Responder n (%)	19 (51.4)	23 (59.0)	20 (48.8)	43 (53.8)
Non-responder n (%)	18 (48.6)	16 (41.0)	21 (51.2)	37 (46.3)
Observation/ Day 99				
n	52	58	57	115
Responder n (%)	16 (30.8)	23 (39.7)	25 (43.9)	48 (41.7)
Non-responder n (%)	36 (69.2)	35 (60.3)	32 (56.1)	67 (58.3)

Upon request, further analyses on efficacy based on Baseline medication use were performed *post hoc*. In MG0003, almost all (191 [95.5%]) study participants reported use of at least 1 baseline MG medication, defined as medications that started prior to dosing and continued after dosing. Per protocol, treatment with corticosteroids and immunosuppressants were to be kept stable throughout the study.

When comparing efficacy results (change from Baseline to Day 43 for MG-ADL [Table 42], QMG [Table 44], and MG-C [Table 46]) across participants with different gMG baseline medications, there were no consistent differences across the 3 efficacy outcome measures between participants treated with corticosteroids, non-steroidal immunosuppressants, parasympathomimetic and the group of patients treated with corticosteroids and/or non-steroidal immunosuppressants. The latter group (n=157) includes participants who were concomitantly treated with steroids and non-steroidal immunosuppressants (n=71), treated with steroids but not with non-steroidal immunosuppressants (n=57) and those who were treated with non-steroidal immunosuppressants but not with steroids (n=29).

When comparing efficacy results (change from Baseline to Day 43 for MG-ADL [Table 43], QMG [Table 45], and MG-C [Table 47]) across participants with different numbers of gMG Baseline medication to treat gMG, there were no consistent differences across the 3 efficacy outcome measures between participants treated with corticosteroids, non-steroidal immunosuppressants, parasympathomimetics and the group of participants treated with corticosteroids and/or non-steroidal immunosuppressants. Participants with no Baseline gMG medication was very low and therefore interpretation of results in this subgroup should be made with caution.

Table 42: MG-ADL scores: observed results and changes from Baseline at Day 43 by background gMG therapy (RS)

Back-ground therapy	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
Corticosteroids for Systemic Use, Plain								
n	38	37	42	41	48	44	90	85
Mean (SD)	8.0 (3.1)	-0.9 (2.8)	8.2 (3.8)	-2.9 (3.2)	8.1 (3.1)	-3.3 (3.4)	8.2 (3.4)	-3.1 (3.3)
Immunosuppressants								
n	32	32	31	30	37	34	68	64
Mean (SD)	9.2 (3.1)	-0.5 (2.7)	7.7 (3.4)	-3.0 (3.4)	8.1 (2.9)	-3.1 (3.4)	7.9 (3.1)	-3.0 (3.4)
Parasympathomimetics								
n	59	58	55	53	57	53	112	106
Mean (SD)	8.6 (3.4)	-0.6 (2.8)	8.4 (3.9)	-3.5 (3.7)	8.0 (2.9)	-3.2 (3.3)	8.2 (3.4)	−3.4 (3.5)
Corticosteroids for Systemic Use, Plain and/or Immunosuppressants								
n	49	48	49	48	59	55	108	103
Mean (SD)	8.5 (3.3)	-0.9 (2.8)	8.2 (3.6)	-3.2 (3.4)	8.0 (3.0)	-3.1 (3.3)	8.1 (3.3)	-3.2 (3.3)

≈=approximate dose; CFB=changes from Baseline; D=day; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; MG-ADL=Myasthenia Gravis-Activities of Daily Living; n=number of study participants; N=total number of study participants in treatment group; Obs=observed values; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation
Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value.
Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability

Table 43: MG-ADL scores: observed results and changes from Baseline at Day 43 by number of background gMG therapies (RS)

No. of background therapies	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
0								
n	3	1	3	3	3	3	6	6
Mean (SD)	7.3	NC	9.7	-2.3	10.0	-4.3	9.8 (2.6)	-3.3 (5.0)
1								
n	17	17	17	16	7	6	24	22
Mean (SD)	8.4 (3.8)	-0.4 (3.3)	8.7 (4.4)	-3.9 (4.1)	8.6 (2.9)	-2.8 (2.6)	8.7 (3.9)	-3.6 (3.7)
2								
n	29	28	27	27	36	34	63	61
Mean (SD)	8.4 (3.4)	-0.9 (2.8)	8.6 (3.7)	-3.9 (3.7)	7.7 (2.7)	-3.0 (3.0)	8.1 (3.2)	-3.4 (3.3)
3								
n	18	18	19	18	21	19	40	37
Mean (SD)	8.7 (3.1)	-0.6 (2.7)	7.6 (3.6)	-2.3 (2.8)	8.4 (3.2)	-3.5 (3.9)	8.0 (3.4)	-2.9 (3.4)

≈=approximate dose; CFB=changes from Baseline; D=day; gMG=generalised myasthenia gravis; MG-ADL=Myasthenia Gravis-Activities of Daily Living; IMP=investigational medicinal product; n=number of study participants; N=total number of study participants in treatment group; NC=not calculated; No.=number; Obs=observed values; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation

Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value. Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability

Table 44: QMG scores: observed results and changes from Baseline at Day 43 by background gMG therapy (RS)

Back-ground therapy	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
Corticosteroids for Systemic Use, Plain								
n	38	37	42	41	48	44	90	85
Mean (SD)	15.6 (3.4)	-1.0 (4.4)	15.7 (3.9)	-4.2 (4.6)	15.5 (3.7)	-6.2 (5.4)	15.6 (3.8)	-5.2 (5.1)
Immunosuppressants								
n	32	32	31	30	37	34	68	64
Mean (SD)	15.7 (3.5)	-0.4 (3.7)	15.5 (3.8)	-4.7 (5.1)	15.6 (3.8)	-4.8 (4.8)	15.6 (3.8)	-4.7 (4.9)
Parasympathomimetics								
n	59	58	55	53	57	53	112	106
Mean (SD)	16.1 (3.6)	-0.8 (4.2)	15.5 (3.7)	-4.2 (4.5)	15.8 (3.7)	-5.9 (5.4)	15.7 (3.7)	-5.1 (5.0)
Corticosteroids for Systemic Use, Plain and/or Immunosuppressants								
n	49	48	49	48	59	55	108	103
Mean (SD)	16.0 (3.5)	-0.6 (4.1)	15.6 (4.0)	-4.5 (4.6)	15.6 (3.8)	-5.8 (5.4)	15.6 (3.9)	-5.2 (5.0)

≈=approximate dose; CFB=changes from Baseline; D=day; n=number of study participants; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; N=total number of study participants in treatment group; Obs=observed values; QMG=Quantitative Myasthenia Gravis; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation
Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value.

Table 45: QMG scores: observed results and changes from Baseline at Day 43 by number of background gMG therapies (RS)

No. of background therapies	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
0								
n	3	1	3	3	3	3	6	6
Mean (SD)	15.0	NC	17.0	-3.0	18.3	-5.3	17.7	-4.2 (4.5)
1								
n	17	17	17	16	7	6	24	22
Mean (SD)	15.4 (3.7)	-2.2 (4.3)	14.1 (2.7)	-3.9 (5.0)	15.1 (2.2)	-3.2 (2.0)	14.4 (2.6)	-3.7 (4.4)
2								
n	29	28	27	27	36	34	63	61
Mean (SD)	16.7 (3.5)	0.0 (3.7)	15.9 (4.5)	-4.8 (4.1)	15.2 (3.9)	-6.2 (5.8)	15.5 (4.1)	-5.6 (5.1)
3								
n	18	18	19	18	21	19	40	37
Mean (SD)	15.1 (3.3)	-1.1 (4.5)	15.8 (3.4)	-4.0 (5.2)	16.1 (3.6)	-5.4 (4.9)	16.0 (3.5)	-4.7 (5.0)

≈=approximate dose; CFB=changes from Baseline; D=day; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; n=number of study participants; N=total number of study participants in treatment group; NC=not calculated; No.=number; Obs=observed values; QMG=Quantitative Myasthenia Gravis; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation
Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value.

Table 46: MG-C scores: observed results and changes from Baseline at Day 43 by background gMG therapy (RS)

Back-ground therapy	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
Corticosteroids for Systemic Use, Plain								
n	38	37	42	41	48	44	90	85
Mean (SD)	14.6 (5.5)	-1.6 (5.2)	16.7 (6.2)	-5.8 (6.4)	17.4 (5.9)	-8.3 (6.7)	17.0 (6.0)	-7.1 (6.7)
Immunosuppressants								
n	32	32	31	30	37	34	68	64
Mean (SD)	15.4 (6.2)	-1.1 (6.2)	15.6 (5.5)	-5.5 (7.3)	16.4 (5.4)	-6.6 (7.0)	16.0 (5.4)	-6.1 (7.1)
Parasympathomimetics								
n	59	58	55	53	57	53	112	106
Mean (SD)	16.3 (6.2)	-1.3 (5.8)	16.0 (6.5)	-5.1 (6.5)	16.7 (5.8)	-7.6 (7.0)	16.3 (6.2)	-6.3 (6.8)
Corticosteroids for Systemic Use, Plain and/or Immunosuppressants								
n	49	48	49	48	59	55	108	103
Mean (SD)	15.5 (6.1)	-1.5 (5.6)	16.3 (6.0)	-5.8 (6.6)	16.8 (5.8)	-7.3 (6.9)	16.6 (5.9)	-6.6 (6.8)

≈=approximate dose; CFB=changes from Baseline; D=day; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; MG-C=Myasthenia Gravis-Composite; n=number of study participants; N=total number of study participants in treatment group; Obs=observed values; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation
Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value

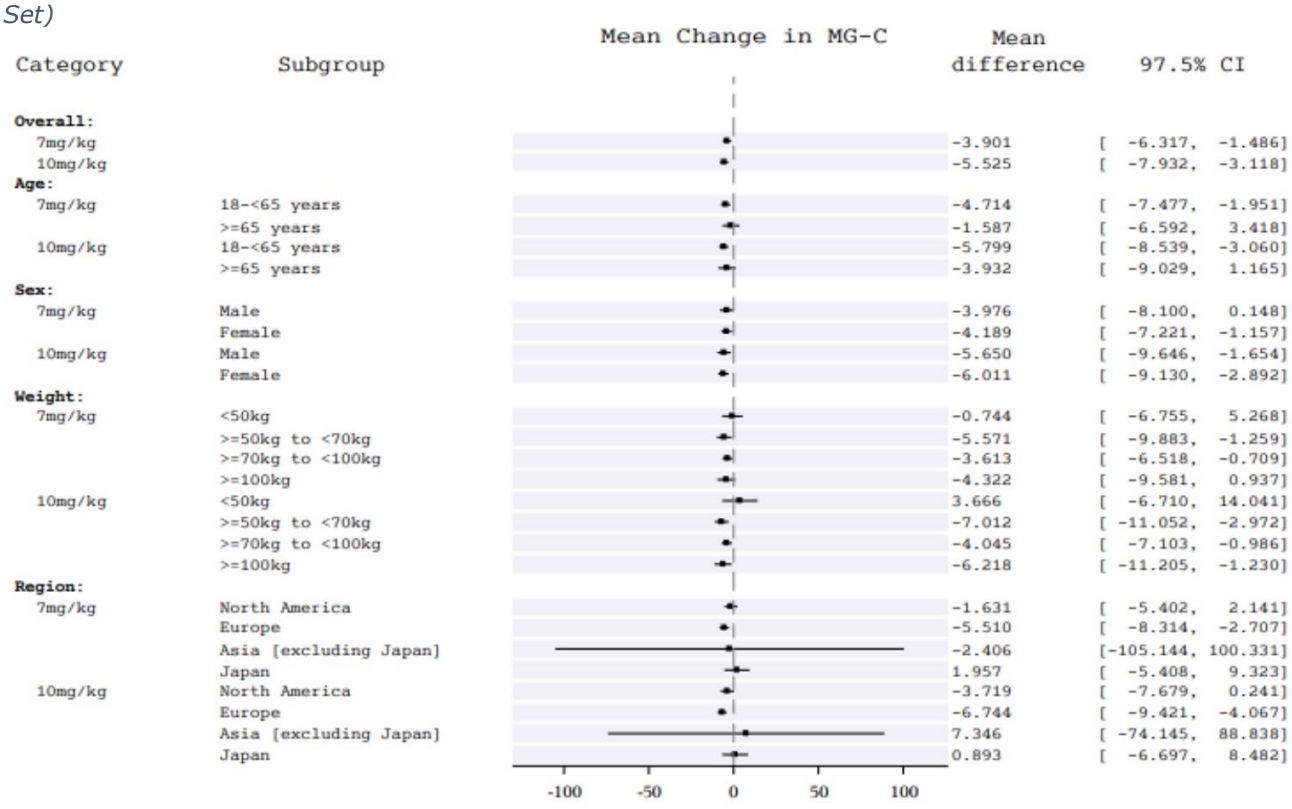
Table 47: MG-C scores: observed results and changes from Baseline at Day 43 by number of background gMG therapies (RS)

No. of background therapies	Treatment group							
	Placebo (N=67)		RLZ ≈7mg/kg (N=66)		RLZ ≈10mg/kg (N=67)		RLZ total (N=133)	
	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)	Baseline (Obs)	D43 (CFB)
0								
n	3	1	3	3	3	3	6	6
Mean (SD)	11.3	NC	14.0	-2.0	15.0	-5.7	14.5 (6.2)	-3.8 (7.3)
1								
n	17	17	17	16	7	6	24	22
Mean (SD)	15.9 (6.8)	-1.9 (5.8)	14.1 (7.5)	-4.1 (6.7)	13.7 (7.6)	-4.0 (7.3)	14.0 (7.3)	-4.1 (6.7)
2								
n	29	28	27	27	36	34	63	61
Mean (SD)	16.6 (6.7)	-1.7 (5.3)	17.6 (5.7)	-6.9 (6.1)	16.3 (5.5)	-7.0 (6.5)	16.9 (5.6)	-6.9 (6.3)
3								
n	18	18	19	18	21	19	40	37
Mean (SD)	14.3 (4.7)	-0.9 (6.3)	15.3 (6.1)	-4.4 (7.2)	17.8 (5.8)	-8.6 (7.4)	16.6 (6.0)	-6.6 (7.5)

≈=approximate dose; CFB=changes from Baseline; D=day; gMG=generalised myasthenia gravis; IMP=investigational medicinal product; MG-C=Myasthenia Gravis-Composite; n=number of study participants; N=total number of study participants in treatment group; No.=number; Obs=observed values; RLZ=rozanolixizumab; RS=randomised set; SD=standard deviation
Note: Baseline is defined as last available predose value prior to the first infusion of IMP in the Treatment Period, or if missing, the Screening value

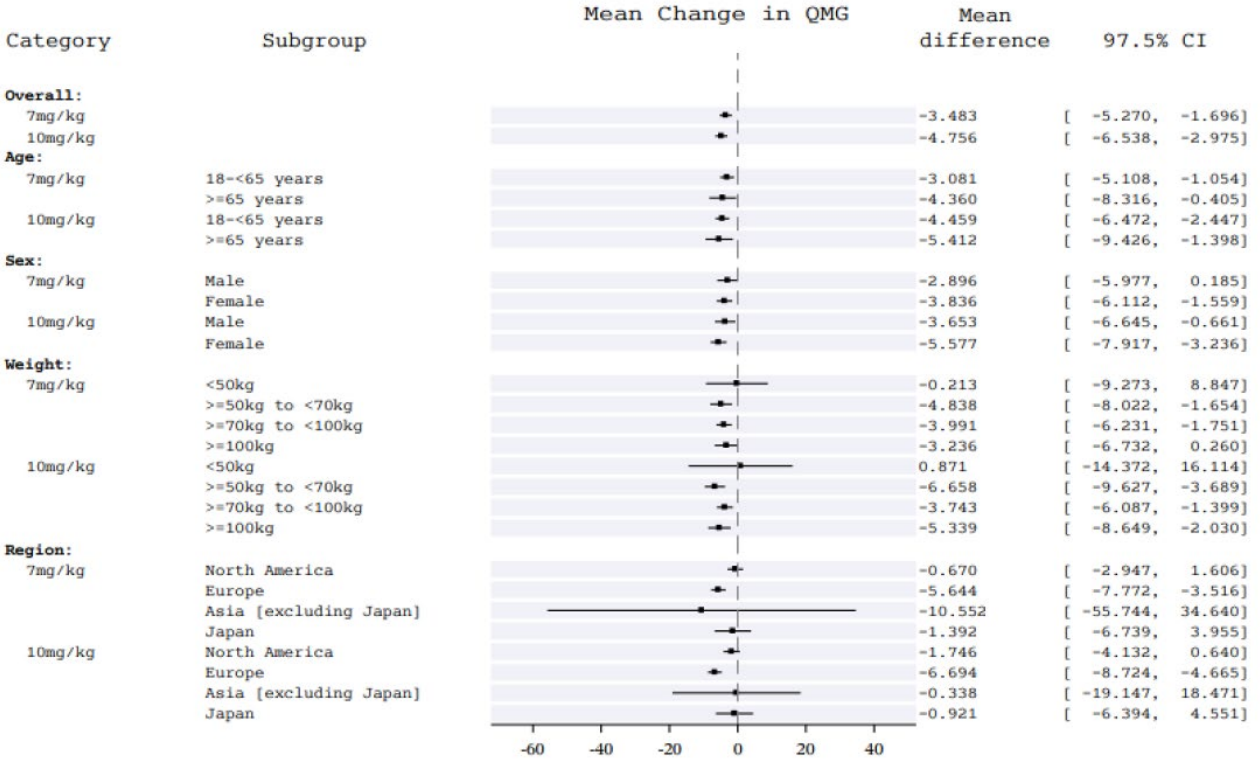
Subgroup analyses of the secondary efficacy endpoints

Figure 20: Forest plot of MG-C change from Baseline to Day 43 (Visit 10) by subgroups (Randomised Set)



AChR=acetylcholine receptor; CI=Confidence Interval; MG-C=Myasthenia Gravis Composite; MuSK=muscle-specific kinase.
Note: A change to the left favors rozanolixizumab.

Figure 21: Forest plot of QMG change from Baseline to Day 43 (Visit 10) by subgroups (Randomised Set)



AChR=acetylcholine receptor; CI=confidence interval; MuSK=muscle-specific kinase; QMG=Quantitative Myasthenia Gravis
Note: A change to the left favors rozanolixizumab.

The **"other" efficacy endpoints** were:

- Use of rescue therapy (IVIg or PEX) due to worsening of gMG symptoms for the Treatment Period and Observation Period

All study participants who needed rescue medication received immunoglobulins.

Placebo group: 3 (4.5%) study participants received rescue treatment during the Treatment Period; 1 (1.5%) of them also received rescue treatment during the Observation Period (57 days after the last infusion).

Rozanolixizumab ≈7mg/kg group: 1 (1.5%) study participant received rescue treatment during the Observation Period (37 days after the last infusion).

Rozanolixizumab ≈10mg/kg group: 2 (3.0%) study participants received rescue treatment during the Observation Period (24 days after the last infusion for 1 study participant and 41 days for the other).

Of note, 59 (29.5%) study participants chose to roll over to the OLE studies MG0004 or MG0007 after completion of the Treatment Period and before the end of the Observation Period and to receive rozanolixizumab instead of opting for permitted rescue therapy (IVIg or PEX) and not rolling over into MG0004 or MG0007.

- Time to first rescue therapy

Table 48: Time to rescue therapy use (IVIg, PLEX) (Randomised set).

	Placebo (N=67)			RLZ ~7mg/kg (N=66)			RLZ ~10mg/kg (N=67)		
Timepoint (days)	Cumulative # Of Events	# At Risk	Survival Estimate	Cumulative # Of Events	# At Risk	Survival Estimate	Cumulative # Of Events	# At Risk	Survival Estimate
8	0	67	100	0	66	100	0	67	100
12	0	67	100	0	65	100	0	67	100
24	2	65	97.01	0	65	100	0	67	100
32	2	64	97.01	0	65	100	0	67	100
43	3	62	95.50	0	65	100	0	67	100
57	3	56	95.50	0	61	100	0	66	100
71	3	50	95.50	0	55	100	1	59	98.46
85	3	45	95.50	1	46	98.08	2	48	96.53
99	3	37	95.50	1	37	98.08	2	36	96.53
Median	NA			NA			NA		
95% CI	NA, NA			NA, NA			NA, NA		
% Censored	95.5			98.5			97.0		
Hazard Ratio [a]				0.286			0.540		
95% CI				0.030, 2.748			0.090, 3.236		
p-value [b]				0.278			0.500		

~=equivalent dose, CI=confidence interval, IVIg=intravenous immunoglobulin G, PEX=plasma exchange, RLZ=Rozanolixizumab.
Note: Participants who discontinue study drug prior to receiving rescue therapy are censored at the date of study drug discontinuation.
Note: Participants who complete the study or are still ongoing without receiving rescue therapy will be censored at the date of their last visit.
[a] A Hazard Ratio >1 indicates Time to rescue therapy is improved for RLZ (~7mg/kg or ~10mg/kg) compared to Placebo.
[b] Comparison of RLZ (~7mg/kg or ~10mg/kg) versus Placebo is made using a Cox Proportional Hazards model including a fixed term for treatment and stratification factor (MuSK+ or AChR+). date of their last visit.

- Time to MG-ADL response

At Day 8, 34.8%, 37.9%, and 23.9% of study participants were MG-ADL responders in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. The highest responder rates were achieved at Day 43 (last measurement in the Treatment Period) for both rozanolixizumab treatment groups with 46 (71.9%) responders in the ≈7mg/kg group and 43 (69.4%) in the ≈10mg/kg group; the highest responder rates were achieved at Day 85 for the placebo group with 20 (31.3%) responders.

At Day 43, 2 (3.0%) study participants in the rozanolixizumab ≈7mg/kg group, 5 (7.5%) in the ≈10mg/kg group, and 3 (4.5%) in the placebo group had missing MG-ADL scores. The proportion of study participants with missing data during the Treatment Period was <10.5% for any treatment group at any visit; the proportion of study participants with missing data during the Observation Period was ≤34.8% for any treatment group at any visit.

The median time to MG-ADL response was 16 days in the rozanolixizumab ≈7mg/kg group, 22 days in the ≈10mg/kg group, and could not be calculated for the placebo group because the Kaplan-Meier plot did not cross at 50%. The hazard ratio for MG-ADL response was 2.114 (95% CI: 1.181, 4.234) and 1.772 (95% CI: 0.989, 3.558) in favour of rozanolixizumab for the ≈7mg/kg and ≈10mg/kg groups, respectively.

- MG-ADL, MG-C, and QMG responders during Treatment and Observation Periods

Table 49:MG-ADL, MG-C and QMG responders at Day 43

	Placebo (N=64)	Rozanolixizumab ≈7 mg/kg (N=64)	Rozanolixizumab ≈10 mg/kg (N=62)
MG-ADL responder, n (%)	20 (31.3 %)	46 (71.9 %)	43 (69.4 %)
MG-C responder, n (%)	26 (40.6 %)	39 (60.9 %)	46 (74.2 %)
QMG responder, n (%)	25 (39.1 %)	35 (54.7 %)	45 (72.6 %)

Percentages are based on the number of participants with non-missing data at Day 43.

- Minimal symptom expression at any time up to Day 43 (Visit 10)

Minimal symptom expression is defined as an MG-ADL total score of 0 or 1, at any time during the Treatment and Observation Periods.

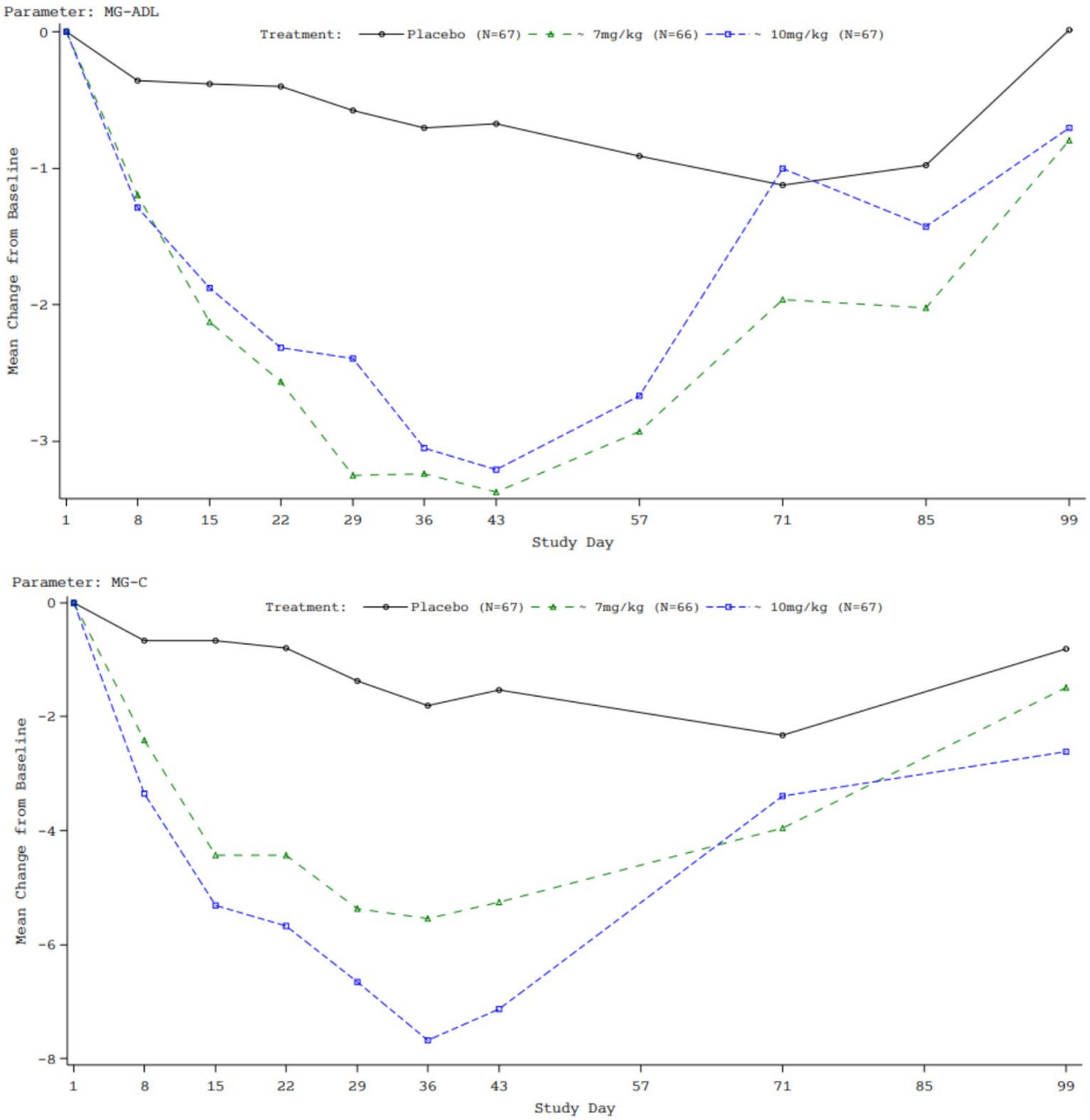
Table 50: Minimal symptom expression at any time during Treatment and Observation Periods (Randomised Set)

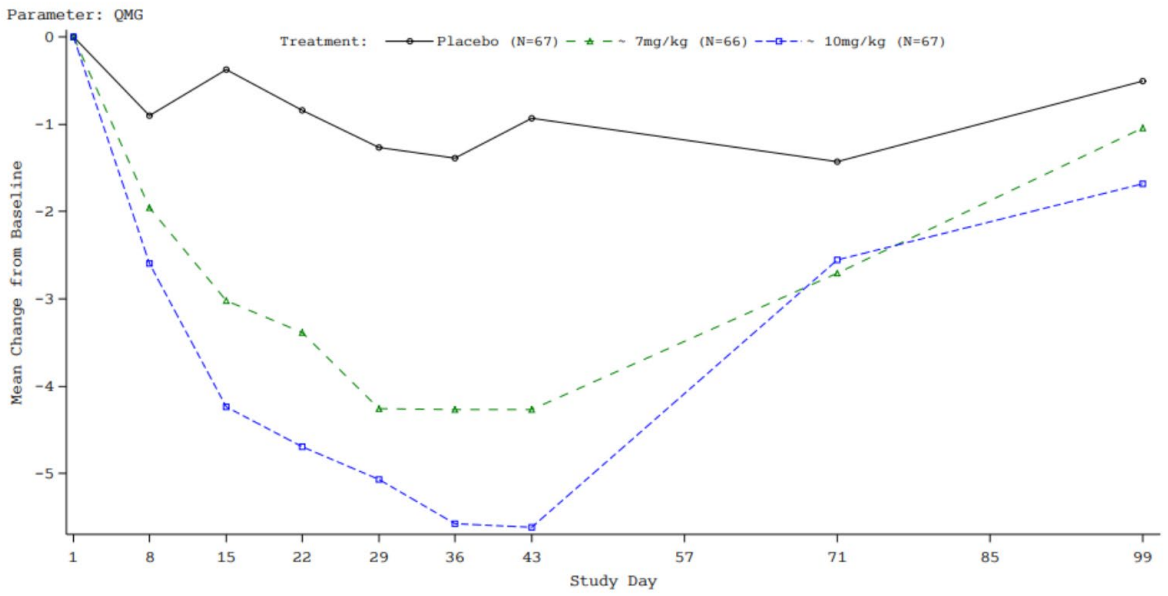
Statistic	Placebo N=67	RLZ ≈7mg/kg N=66	RLZ ≈10mg/kg N=67
n	67	66	67
Yes, n (%)	2 (3.0)	17 (25.8)	19 (28.4)

≈=equivalent dose; MG-ADL=Myasthenia Gravis Activities of Daily Living; N=total number of study participants in treatment group; RLZ=rozanolixizumab Note: Percentages are based on the number of study participants with MG-ADL data in the Randomised Set. Note: Minimum Symptom Expression was defined as achieving an MG-ADL total score of 0 or 1

- Change from Baseline at each scheduled assessment during the Treatment Period and Observation Period in MG-ADL, MG-C, and QMG scores (including and excluding ocular items for all 3), and in MG Symptoms PRO "Muscle Weakness Fatigability", "Physical Fatigue", "Bulbar Muscle Weakness", "Respiratory Muscle Weakness", and "Ocular Muscle Weakness" scores.

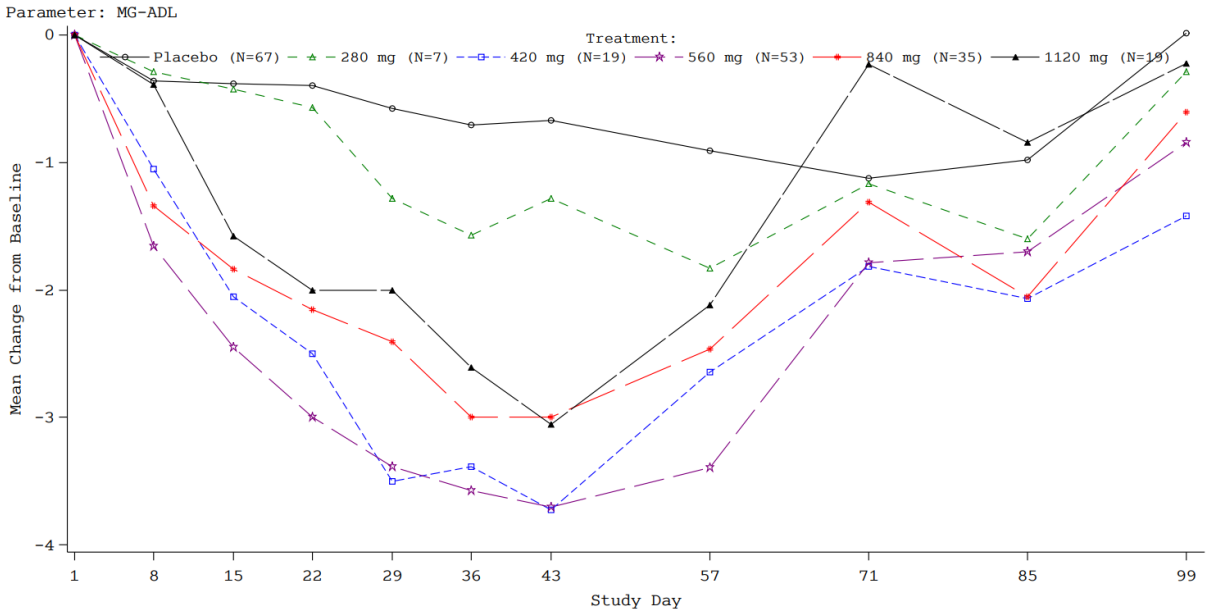
Figure 22: Mean change from Baseline in MG-ADL, MG-C, QMG by treatment (Randomised Set)

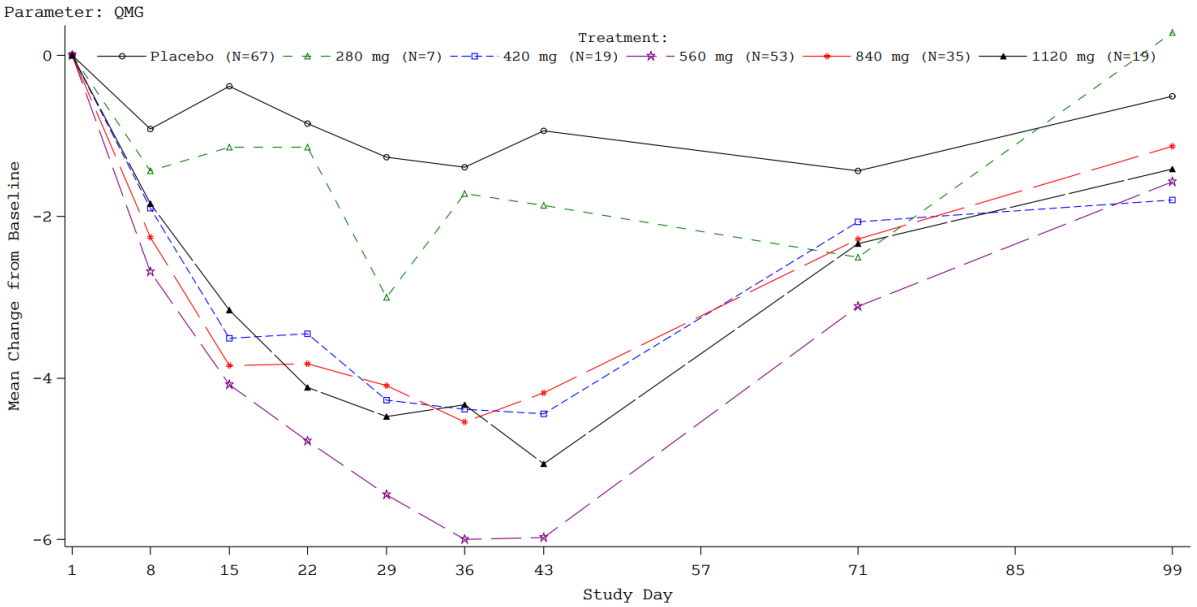


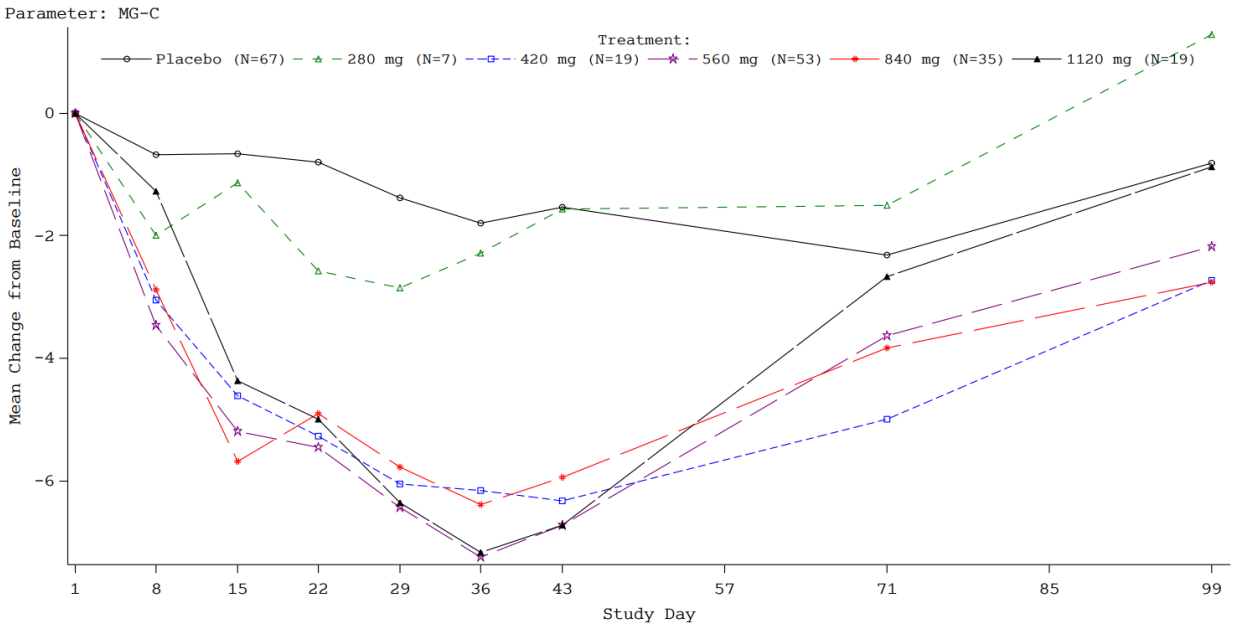


- Mean Change from Baseline in MG-ADL, QMG, MG-C by Administered Dose (Randomised Set)

Figure 23: Mean Change from Baseline in MG-ADL, QMG, MG-C and MG Symptom PRO by Administered Dose Analysis Set (Randomised Set)







~=equivalent dose, MG-C=myasthenia gravis composite, MG-ADL=myasthenia gravis activities of daily living, QMG=quantitative myasthenia gravis, RLZ=rozanolixizumab

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients with Generalized Myasthenia Gravis			
Study identifier	Study number: MG0003 EudraCT Number: 2019-000968-18 NCT Number: NCT03971422		
Design	Randomised, multicentre, 2-stage, double-blind, parallel-group, placebo-controlled, stratified by MuSK+ and AchR+, efficacy, safety and tolerability study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		14 weeks double-blind: 6-week Treatment Period and an 8-week Observation Period Up to 4-week Screening Period not applicable
Hypothesis	Superiority		
Treatments groups	Rozanolixizumab (RLZ) ≈7mg/kg		Rozanolixizumab ≈7mg/kg Total of 6 subcutaneous infusion administered at 1-week intervals Study participants randomised: 66
	Rozanolixizumab (RLZ) ≈10mg/kg		Rozanolixizumab ≈10mg/kg Total of 6 subcutaneous infusion administered at 1-week intervals Study participants randomised: 67
	Placebo		Placebo Total of 6 subcutaneous infusion administered at 1-week intervals Study participants randomised: 67
Endpoints and definitions	Primary endpoint	CFB in MG-ADL at Day 43	Change from Baseline (CFB) to Day 43 in MG-activities of daily living (ADL) score
	Secondary endpoint	CFB in MG-C at Day 43	Change from Baseline to Day 43 in the MG-Composite (MG-C) score
	Secondary endpoint	CFB in QMG at Day 43	Change from Baseline to Day 43 in quantitative myasthenia gravis (QMG) score
	Secondary endpoint	CFB in MG Symptoms PRO 'Muscle Weakness Fatigability'	Change from Baseline to Day 43 in the MG Symptoms patient-reported outcome (PRO) 'Muscle Weakness Fatigability' score
	Secondary endpoint	CFB in MG Symptoms PRO 'Physical Fatigue'	Change from Baseline to Day 43 in the MG Symptoms PRO 'Physical Fatigue' score
	Secondary endpoint	CFB in MG Symptoms PRO 'Bulbar Symptoms'	Change from Baseline to Day 43 in the MG Symptoms PRO 'Bulbar Symptoms' score
	Secondary endpoint	MG-ADL responder at Day 43	MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43
Database lock eCRF data	12 Nov 2021		

Results and Analysis For all primary and secondary endpoints, subject to pre-specified statistical testing, for both Rozanolixizumab groups, statistically significant differences to placebo were demonstrated.				
Analysis description	Primary Analysis			
Analysis population and time point description	Randomised Set (RS), which consisted of all study participants who were randomised, using their randomised treatment group Main time point of interest is Day 43, which is 1 week after the 6th infusion			
	Treatment group	Placebo	Rozanolixizumab ≈7mg/kg	Rozanolixizumab ≈10mg/kg
	Number of participants	67	66	67
Estimate, variability, and effect estimate per comparison	CFB in MG-ADL at Day 43 (LS Mean (SE))	-0.784 (0.488)	- 3.370 (0.486)	-3.403 (0.494)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-2.586	-2.619
	Confidence interval		-4.091, -1.249	-3.994, -1.163
	P-value		<0.001	<0.001
	CFB in MG-C at Day 43 (LS Mean (SE))	-2.029 (0.917)	-5.930 (0.916)	-7.554 (0.934)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-3.901	-5.525
	Confidence interval		-6.634, -1.245	-8.303, -2.968
	P-value		<0.001	<0.001
	CFB in QMG at Day 43 (LS Mean (SE))	-1.915 (0.682)	-5.398 (0.679)	-6.672 (0.692)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-3.483	-4.756
	Confidence interval		-5.614, -1.584	-6.821, -2.859
	P-value		<0.001	<0.001
	CFB in MG Symptoms PRO 'Muscle Weakness Fatigability' (LS Mean (SE))	-10.588 (3.034)	-23.029 (3.034)	-25.751 (3.095)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-12.441	-15.163
	Confidence interval		-21.804, -4.089	-23.596, -6.450
	P-value		<0.001	<0.001

	CFB in MG Symptoms PRO 'Physical Fatigue' (LS Mean (SE))	-10.637 (3.051)	-19.287 (3.046)	-25.459 (3.107)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-8.650	-14.822
	Confidence interval		-18.058, -0.134	-23.759, -5.936
	P-value		0.012	<0.001
	CFB in MG Symptoms PRO 'Bulbar Symptoms' (LS Mean (SE))	-3.519 (2.397)	-14.839 (2.406)	-14.224 (2.464)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-11.320	-10.705
	Confidence interval		-18.958, -4.998	-17.787, -3.998
	P-value		<0.001	<0.001
	MG-ADL responder at Day 43 (n (%))	19 (28.4)	45 (68.2)	41 (61.2)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Odds Ratio vs Placebo		5.765	4.273
	Confidence interval		2.100, 14.882	1.653, 11.791
	P-value		<0.001	<0.001
Notes	All p-values and confidence intervals are based on a stagewise combination test; Although pre-specified, statistical test for MG-ADL responder was not included in hierarchical test procedure.			
Analysis description	Subgroup analysis by MG-specific autoantibodies, MuSK+ and AChR+ The subgroup analysis was pre-specified, and the importance of the subgroup is already reflected in the design of the study where autoantibodies were utilised as the only stratification factor.			
Estimate, variability, and effect estimate per comparison	Treatment group	Placebo	Rozanolixizumab ≈7mg/kg	Rozanolixizumab ≈10mg/kg
	Number of participants Subgroup: MuSK+	8	5	8
	CFB in MG-ADL at Day 43 (LS Mean (SE))	2.283 (1.945)	-7.275 (1.943)	-4.163 (1.775)
	Comparison groups		Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo		-9.558	-6.446
	Confidence interval		-15.246, -3.870	-11.030, -1.862
	Number of participants Subgroup: AChR+	55	59	58
	CFB in MG-ADL at Day 43 (LS Mean (SE))	-1.095 (0.872)	-3.032 (0.885)	-3.355 (0.870)

	Comparison groups	Rozanolixizumab ≈7mg/kg and Placebo	Rozanolixizumab ≈10mg/kg and Placebo
	Difference vs Placebo	-1.937	-2.260
	Confidence interval	-3.063, -0.811	-3.385, -1.134

Title: An Open-label Extension Study to Evaluate Rozanolixizumab in Study Participants with Generalized Myasthenia Gravis			
Study identifier	Study number: MG0007 EudraCT Number: 2020-003230-20 NCT Number: NCT04650854		
Design	Multicentre, randomised, open-label extension study to evaluate the long-term safety, tolerability, and efficacy of repeated 6-week treatment cycles of rozanolixizumab based on myasthenia gravis worsening		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Ongoing Study start: 03 Feb 2021 Interim data cut off: 08 Jul 2022 0 up to 4 weeks rollover period not applicable
Hypothesis	Not applicable		
Treatments groups	Rozanolixizumab (RLZ) ≈7mg/kg		Rozanolixizumab ≈7mg/kg Treatment cycle of 6 subcutaneous infusion administered at 1-week intervals; repeated based on MG symptom needs Study participants randomised: 88
	Rozanolixizumab (RLZ) ≈10mg/kg		Rozanolixizumab ≈10mg/kg Treatment cycle of 6 subcutaneous infusion administered at 1-week intervals; repeated based on MG symptom needs Study participants randomised: 77
Endpoints and definitions	Secondary endpoint	CFB to Day 43 in MG-ADL by cycle	Change from Baseline (Day 1) to Day 43 in MG-ADL for each Treatment Cycle
	Secondary endpoint	MG-ADL responder at Day 43 by cycle	MG-ADL responder (≥2.0-point) at Day 43 for each treatment cycle
	Secondary endpoint	Time to MG-ADL response	Time to MG-ADL response (in days) by study cycle
	Secondary endpoint	Treatment-free interval	Time between consecutive treatment cycles (last dose of previous cycle to 1st dose of next cycle)
Database lock (Interim cut)	08 Jul 2022		
Results and Analysis			
Analysis description	Secondary Analysis		
Analysis population and time point description	All efficacy analyses are presented for the safety set by study cycle and dose level received within the cycle.		

Descriptive statistics and estimate variability	Treatment group	Rozanolixizumab ≈7mg/kg	Rozanolixizumab ≈10mg/kg
	Number of participants	N=79	N=78
	MG-ADL score change from Baseline to Day 43 during each treatment cycle Mean (SD)		
	Cycle 1	n=73	n=67
		-3.6 (3.4)	-3.2 (3.2)
	Cycle 2	n=50	n=63
		-3.0 (3.1)	-3.8 (3.9)
	Cycle 3	n=35	n=48
		-3.4 (2.7)	-3.4 (3.3)
	Cycle 4	n=29	n=36
		-4.2 (2.9)	-3.3 (3.2)
	MG-ADL responder (≥2.0-point) at Day 43 for each treatment cycle (observed) n (%)		
	Cycle 1	n=73	n=67
		54 (74.0)	43 (64.2)
	Cycle 2	n=50	n=63
		33 (66.0)	43 (68.3)
	Cycle 3	n=35	n=48
		27 (77.1)	33 (68.8)
	Cycle 4	n=29	n=36
		25 (86.2)	22 (61.1)
	Time to MG-ADL response (days) by study cycle median (95% CI)		
	Cycle 1	n=79	n=78
		10 (8, 15)	23 (15, 41)
	Cycle 2	n=54	n=67
		15 (9, 17)	15 (9, 22)
	Cycle 3	n=41	n=55
		15 (9, 15)	14 (8,16)
	Cycle 4	n=31	n=39
		9 (8, 15)	14 (9,27)

	Treatment-free interval (days) Median (95% CI)		
	Between Cycle 1 and 2	n=79	n=78
		64 (50, 86)	64 (43, 99)
	Between Cycle 2 and 3	n=54	n=67
		57 (43, 67)	46 (37, 62)
	Between Cycle 3 and 4	n=41	n=55
		37 (35, 50)	38 (36, 43)
	Between Cycle 4 and 5	n=31	n=39
		35 (30, 47)	36 (31, 37)
Analysis description	Subgroup analysis by MG-specific autoantibodies, MuSK+ and AChR+ The subgroup analysis was pre-specified		
Descriptive statistics and estimate variability	anti-MuSK+ participants: MG-ADL score change from Baseline to Day 43 during each treatment cycle Mean (SD) or Min, Max (if n<3)		
	Cycle 1	n=8	n=1
		-5.5 (3.0)	-2, -2
	Cycle 2	n=6	n=2
		-4.2 (4.0)	-12, -3
	Cycle 3	n=4	n=1
		-3.8 (2.6)	-4, -4
	Cycle 4	n=3	n=1
		-4.3 (N/A)	1, 1
	anti-AchR+ participants: MG-ADL score change from Baseline to Day 43 during each treatment cycle Mean (SD)		
	Cycle 1	n=62	n=62
		-3.4 (3.5)	-3.4 (3.2)
	Cycle 2	n=41	n=57
		-2.8 (3.2)	-3.9 (3.9)
	Cycle 3	n=27	n=45
		-3.7 (2.7)	-3.4 (3.4)
	Cycle 4	n=24	n=32
		-4.3 (3.1)	-3.6 (3.2)

2.6.5.3. Clinical studies in special populations

Around 25% of all individuals enrolled in the MG0003 study were ≥65 years of age.

Table 51: Number of elderly participants in MG0003 and Pool E1

	Age 65-74 years	Age 75-84 years	Age 85+ years
	N/total (%)		
MG0003	33/200 (16.5%)	14/200 (7.0%)	2/200 (1.0%)
Pool E1	17/127 (13.4%)	8/127 (6.3%)	1/127 (0.8%)

The subgroup analysis of the primary endpoints showed no marked difference in the primary endpoints (MG-ADL change from Baseline to Day 43) for the participants of ≥65 years of age compared to those of <65 years of age in both rozanolixizumab treatment groups. Of note, participants in the elderly population (≥65 years of age) worsened under placebo (LS mean MG-ADL score of 0.776) while in the younger population (<65 years of age), a placebo response (improvement) was observed (LS mean MG-ADL score of -0.988).

Table 52: MG-ADL change from baseline to Day 43 by age (Randomised Set)

	MG-ADL change from baseline to Day 43					
	<65 years			≥65 years		
Statistic	Placebo N=51	RLZ ≈7mg/kg N=49	RLZ ≈10mg/kg N=51	Placebo N=16	RLZ ≈7mg/kg N=17	RLZ ≈10mg/kg N=16
n	47	48	49	15	17	16
LS Mean (SE)	-0.988 (0.530)	-3.565 (0.524)	-3.755 (0.536)	0.776 (1.130)	-1.511 (1.257)	-1.078 (1.224)
Difference vs Placebo [a]		-2.577	-2.767		-2.287	-1.853
97.5% CI for difference [b]		-3.960, -1.195	-4.134,-1.401		-5.187, 0.613	-4.686, 0.979

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Long-term response – cyclic treatment

To explore clinical response in gMG patients following repeated 6-week cyclic treatment with rozanolixizumab, data from MG0003 were pooled with the OLE studies, MG0007 and MG0004 (first 6 weeks).

Table 53: Overview of efficacy pools

Pool name/description	Studies (data utilized)	Treatments groups	Analysis Population Size	Purpose of pool
Pool E1/ ISAP Amendment 1 Section 3.1.1.1 **Study participants having at least 2 symptom-driven cycles**	MG0003 (placebo data are excluded) MG0004 (first 6 weeks, for study participants requiring rescue therapy in the Observation Period of MG0003) MG0007 (only symptom-driven cycles)	For each cycle: ≈7mg/kg, ≈10mg/kg, RLZ total	First 2 cycles: N=127	To assess the response after each symptom-driven treatment cycle
Pool E2/ ISAP Amendment 1 Section 3.1.1.2 **Study participants having/waiting for the first symptom-driven cycle after rozanolixizumab treatment**	MG0003 (placebo data are excluded) MG0004 (first 6 weeks, for study participants requiring rescue therapy in Observation Period of MG0003) MG0007 (only symptom-driven cycles)	Last rozanolixizumab treatment before a symptom-driven cycle: ≈7mg/kg, ≈10mg/kg RLZ total	N=167	To assess the time to retreatment
Pool E3/ ISAP Amendment 1 Section 3.1.1.3 **Study participants having at least 2 consecutive symptom-driven cycles**	MG0003 (placebo data are excluded) MG0007 (only symptom-driven cycles)	For each cycle: ≈7mg/kg, ≈10mg/kg RLZ total	N=110	To assess the response after each symptom-driven treatment cycle, without any maintenance or fixed treatment in-between

≈: approximate dose; gMG: generalised myasthenia gravis; ISAP: integrated statistical analysis plan; N: number of study participant. RLZ total: rozanolixizumab ≈7mg/kg and rozanolixizumab ≈10mg/kg combined.
Note: Symptom-driven cycle is defined as a cycle for which decision for the treatment was based on the gMG symptom worsening (investigator's judgment with guidance to consider an increase of 2.0 points on the MG-ADL or 3.0 points on the QMG scale).

Kaplan Meier analyses were conducted in Pool E2 to explore the treatment-free interval (i.e., the time between the last infusion of rozanolixizumab to the first infusion of the next symptom driven cycle) (Table 54). The estimated median treatment-free interval to the first symptom-driven cycle was ~9 weeks (i.e., 63 days) for the overall population. The probability for participants to achieve treatment-free intervals of at least 15 weeks (105) days was >25%, reflecting the durability of response to rozanolixizumab treatment. For the participants with frequent treatment cycles, the treatment-free intervals remained stable over time (5 to 7 weeks).

Irrespective of the treatment cycle, most study participants had treatment-free intervals between 4 and 13 weeks. Of note, from cycle to cycle, ~10% of the study participants had a treatment-free interval <4 weeks (Table 55).

Table 54: Estimated median (Kaplan-Meier) of the time to symptom-driven cycle (rozanolixizumab total, Pool E2)

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
First cycle				
n	167	-	-	-
Median[a] (Q1,Q3)	63 (36, 105)	-	-	-
censored[b]	23	-	-	-
Participants had 1st cycle and having/waiting 2nd cycle				
N	144	144	-	-
Median[a] Q1,Q3)	51 (36, 72)	64 (36, 121)	-	-
censored[b]	-	35	-	-
Participants had 2nd cycle and having/waiting 3rd cycle				
n	109	109	109	-
Median[a] (Q1,Q3)	44 (36, 64)	45 (35, 80)	43 (35, 69)	-
censored[b]	-	-	22	-
Participants had 3rd cycle and having/waiting 4th cycle				
n	87	87	87	87
Median[a] (Q1,Q3)	43 (35, 64)	43 (32, 65)	38 (30, 62)	37 (30, 55)
censored[b]	-	-	-	24

n=number of study participants; N=total number of study participants in treatment group; Q=quartile; RLZ=rozanolixizumab

[a] Kaplan-Meier estimate (days)

[b] Participants without a symptom-driven cycle (Cycle 1) or subsequent symptom-driven cycles (Cycles 2, 3, 4) after RLZ treatment (waiting for a 2nd, 3rd, or a 4th symptom-driven cycle, respectively) are censored at time of dropping-out, data cutoff date, or end of MG0007); the participants who had a previous cycle already censored are not included.

Notes: The time of retreatment is defined as date of first RLZ infusion in consecutive cycle minus date of last infusion before new cycle +1 (or date of censoring minus date of last infusion before potential new cycle +1). Data for additional cycles and by rozanolixizumab treatment group can be found in ISE Tables.

Table 55: Frequency of time to symptom-driven cycle (rozanolixizumab total, Pool E2)

Category (weeks)	Time to Cycle 1 n (%)	Time between Cycles 1 and 2 n (%)	Time between Cycles 2 and 3 n (%)	Time between Cycles 3 and 4 n (%)
<4[a]	15 (9.0)	11 (7.6)	7 (6.4)	8 (9.2)
≥4 to <13	99 (59.3)	76 (52.8)	71 (65.1)	53 (60.9)
≥13 to <26	23 (13.8)	17 (11.8)	9 (8.3)	2 (2.3)
≥26 to <39	6 (3.6)	4 (2.8)	0	0
≥39 to <52	1 (0.6)	1 (0.7)	0	0
≥52	0	0	0	0
Censored[b]	23 (13.8)	35 (24.3)	22 (20.2)	24 (27.6)

≈=approximate dose; N=study participants within the respective RLZ treatment group before symptom-driven cycle; RLZ=rozanolixizumab

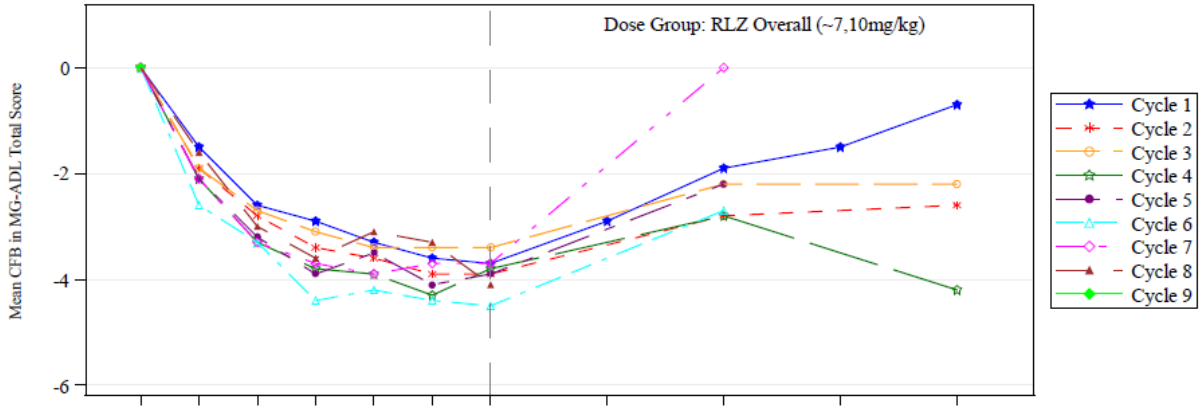
[a] Interval below the recommended interval between 2 cycles (4 cycles). Descriptive statistics for interval <4 weeks are provided ISE Table 3.12.5.1, interval ranged between 10 and 27 days with the shortest interval observed between the 1st and 2nd symptom-driven cycles.

[b] Participants without a 1st symptom-driven cycle after RLZ treatment (time to Cycle 1), 2nd symptom-driven (time between Cycle 1 and Cycle 2), 3rd symptom-driven (time between Cycle 2 and Cycle 3) or 4th symptom-driven (time between Cycle 3 and Cycle 4) were censored at time of dropping-out, data cutoff date, or end of the study (MG0003 or MG0007).

Notes: The time to retreatment is defined as date of first RLZ infusion in consecutive cycle minus date of last infusion before new cycle +1 (or date of censoring minus date of last infusion before potential new cycle +1). Data for additional cycles and by rozanolixizumab treatment group can be found in ISE Tables.

The consistency of response with repeated cyclic treatments with rozanolixizumab was evaluated with respect to impact on MG-ADL, MG-C, and QMG scores. For each 6-week treatment cycle and observation period, change from Baseline to each scheduled assessment in MG-ADL score, QMG score, and MG-C score showed consistent improvement, represented by a decrease in the score at Day 43 for each cycle. Figure 26 represents the mean change from Baseline in MG-ADL scores over time for each cycle for Pool E1.

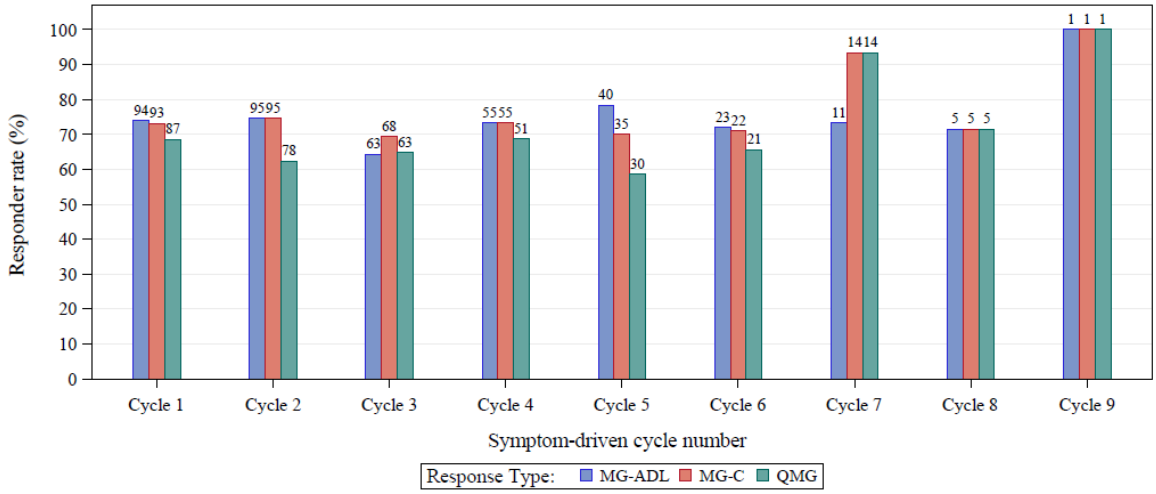
Figure 24: Mean change from baseline in MG-ADL scores to each scheduled assessment by cycle



Day	1	8	15	22	29	36	43	57	71	85	99
Number of Participants at Visit											
Cycle 1	127	120	117	118	123	117	127	80	85	57	94
Cycle 2	127	108	112	110	125	112	127		66		39
Cycle 3	98	94	95	97	97	95	98		48		21
Cycle 4	75	75	74	70	72	73	75		30		5
Cycle 5	51	48	49	50	48	48	51		13		1
Cycle 6	32	30	32	30	32	32	32		7		
Cycle 7	15	15	14	15	14	15	15		4		1
Cycle 8	7	7	7	7	7	7	7				
Cycle 9	1	1	1	1	1	1	1				

Responder rates at Day 43 of Cycle 1 were >70 % for MG-ADL and MG-C and close to 70% for QMG (Figure 25).

Figure 25: MG-ADL, MG-C, and QMG response rate at Day 43 by cycle



MG-ADL=Myasthenia Gravis-Activities of daily Living; MG-C= Myasthenia Gravis Composite score; QMG=quantitative Myasthenia Gravis.
Numbers on top of bar represents the number of study participants with a response.
Responder is a participant with an improvement in a particular score from Baseline at the given visit without use of rescue medication.

During the first cycle, 35 (27.6 %) study participants achieved MSE (MG-ADL score of 0 or 1 acquired at any visit during the Treatment Period and Observation Period without the use of rescue therapy). A

substantial proportion of patients reaching MSE were observed following each repeated cyclic treatment with MSE remaining more than 25 % of the participants.

With repeated cyclic treatment, onset of MG-ADL response was consistently seen in at least approximately 40 % of participants as early as Day 8 following the first rozanolixizumab administration, and the median to response (i.e., when response is observed for around 50% of the study population) remained consistently about 2 weeks.

Table 56: MG-ADL, MG-C and QMG scores: observed results and changes from baseline at Day 43, by historical anti-autoantibody status (Pool E1)

	MG-ADL				MG-C				QMG			
Subgroup	**Anti-MuSK+ N=12**		**Anti-AChR+ N=115**		**Anti-MuSK+ N=12**		**Anti-AChR+ N=115**		**Anti-MuSK+ N=12**		**Anti-AChR+ N=115**	
Timepoint	**n**	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**
Cycle 1												
BL (Obs.)	12	10.9 (3.4)	115	8.7 (3.6)	12	21.0 (7.4)	115	17.0 (6.3)	12	17.3 (4.9)	115	16.1 (4.0)
D43 (CFB)	12	-7.0 (3.5)	115	-3.4 (3.3)	12	-13.8 (6.6)	115	-6.7 (6.4)	12	-9.4 (3.9)	115	-5.0 (4.7)
Cycle 2												
BL (Obs.)	12	10.8 (3.1)	115	8.8 (3.8)	12	19.8 (5.6)	115	16.4 (7.1)	12	16.6 (4.3)	114	15.7 (4.7)
D43 (CFB)	12	-5.7 (3.9)	115	-3.7 (3.4)	12	-10.8 (8.1)	114	-7.1 (6.4)	12	-7.0 (3.6)	113	-4.5 (4.7)
Cycle 3												
BL (Obs.)	7	10.6 (5.3)	91	8.8 (3.4)	7	19.7 (10.5)	91	16.2 (6.8)	7	19.7 (10.0)	91	15.4 (4.8)
D43 (CFB)	7	-4.7 (3.3)	91	-3.3 (3.3)	7	-8.0 (5.7)	90	-6.3 (6.5)	7	-10.0 (6.1)	90	-4.3 (4.6)
Cycle 4												
BL (Obs.)	6	9.8 (3.3)	69	8.8 (3.5)	6	15.8 (5.5)	69	17.5 (7.3)	6	16.0 (4.7)	69	15.8 (5.4)
D43 (CFB)	6	-4.2 (2.4)	69	-3.8 (3.5)	6	-6.5 (5.6)	69	-7.8 (7.6)	6	-6.7 (5.4)	68	-5.1 (5.3)

≈=approximate dose; CFB=changes from Baseline; D=day; MG-ADL=Myasthenia Gravis-Activities of Daily Living MG-C=Myasthenia Gravis-Composite; n=number of study participants; N=total number of study participants in treatment group; Obs=observed values; QMG=Quantitative Myasthenia Gravis; RLZ=rozanolixizumab; SD=standard deviation

Note: Efficacy data collected at or after the time point of rescue use are excluded from the analysis with no imputation of missing data.

Only the first 4 cycles for the overall population are presented here; data for additional cycles and by dose group can be found in ISE Tables.

An increase in the incidence of ADA including Nab was observed in gMG study participants following repeated cyclic treatment. However, the presence of ADA or Nab had no impact on the mean change from Baseline in MG-ADL score at Day 43 (Table 57). In Cycles 1 through 4, participants who were TE-ADA and Nab positive demonstrated a similar or greater mean MG-ADL response as participants who were ADA-negative.

Table 57: Mean change from baseline in MG-ADL score at Day 43 by ADA participant category (Pool S3)

	Cycle 1 N=168		Cycle 2 N=98		Cycle 3 N=73		Cycle 4 N=56	
	Nsub	Mean CFB	Nsub	Mean CFB	Nsub	Mean CFB	Nsub	Mean CFB
ADA Category[a]								
ADA-NEG	77	-3.70	35	-3.34	29	-2.62	14	-1.93
Inconclusive								
TE-POS, Nab-POS	13	-3.54	15	-4.40	21	-3.05	16	-3.87
TE-POS, Nab-NEG	14	-3.50	8	-3.88	8	-1.75	5	-4.80

≈=approximate dose; ADA=anti-drug antibodies; CFB=change from Baseline in MG-ADL score; MG-ADL=Myasthenia Gravis-Activities of Daily Living; N=study participants in each cycle; Nsub=number of study participants within ADA category. NEG=negative; POS=positive; TE=Treatment emergent
[a] ADA category definition is provided in ISI Section 6.2.1.2. None of the participant was categorized as Non-TE-POS, Nab-POS, or Nab-NEG
Note: Pool S3 and E1 is utilizing MG-ADL data from participants from pool E1 who are in both pools.

2.6.5.6. Supportive study(ies)

Two OLE studies evaluated long-term safety, tolerability and efficacy of rozanolixizumab administered as 6-week treatment cycles based on clinical needs (MG0007) or administered weekly (MG0004).

MG0007

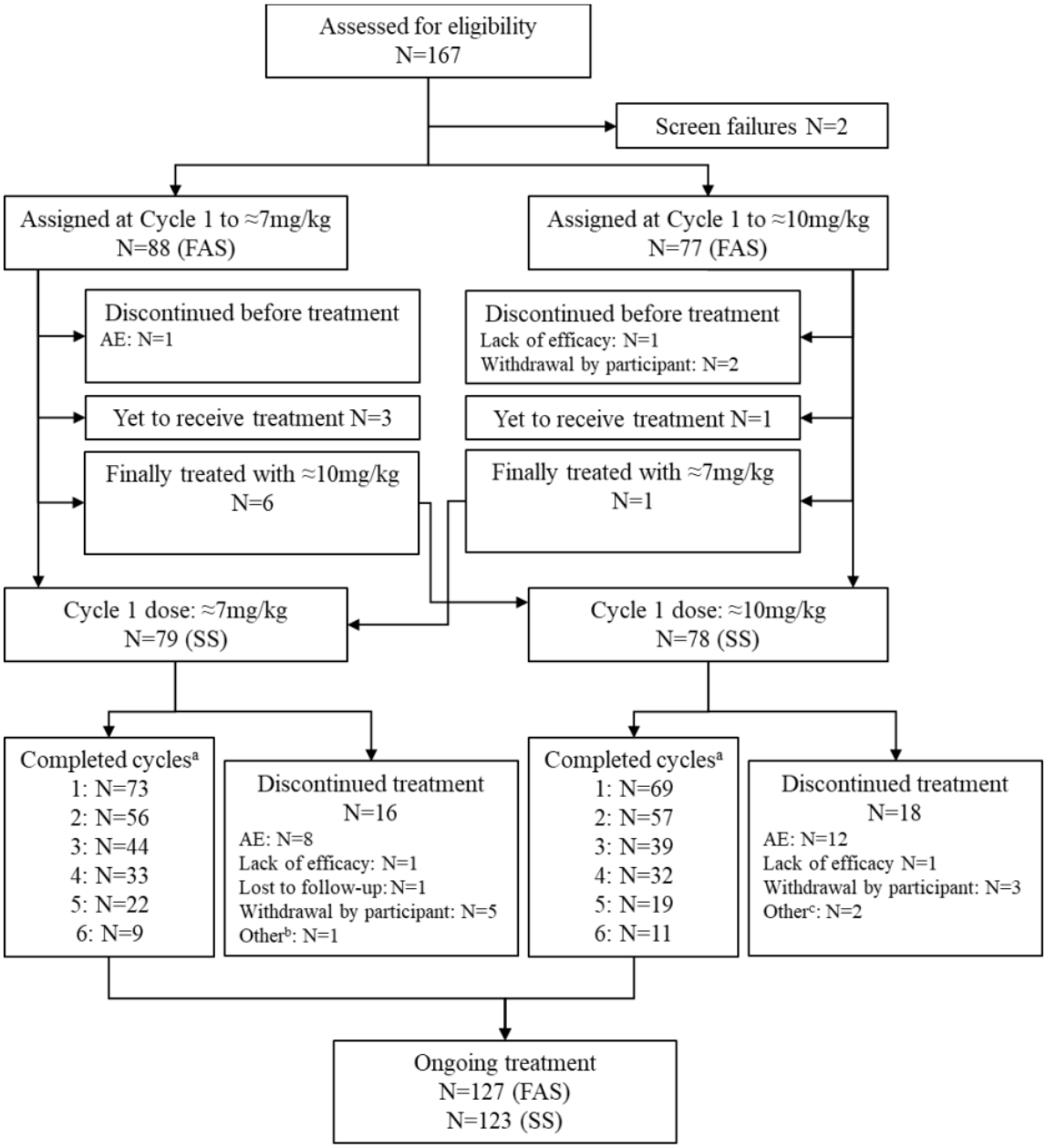
The ongoing study MG0007 enrolled 165 patients who rolled over from MG0003 (105) and MG0004 (60) studies (35 participants having received placebo in MG0003 rolled over directly to MG0007).

Each cycle consisted of 6 weeks of treatment followed by an observation period. Initiation of additional treatment cycles were based on clinical evaluation of gMG symptoms. Four weeks were to be maintained between cycles unless IgG levels returned to ≥ 2 g/L within the 4 weeks, then additional treatment cycles could be initiated earlier.

Respectively 88 (52 from MG0003 and 36 from MG0004) and 77 (53 from MG0003 and 24 from MG0004) study participants were assigned to the ≈7mg/kg and ≈10mg/kg rozanolixizumab treatment groups in cycle 1. At the time of data-cutoff for the interim CSR (08 Jul 2022), 157 study participants had received rozanolixizumab in their first MG0007 cycle (safety set); no participants had completed the study, most of them (n=123) were ongoing in the study and 34 had discontinued the study (21.7%). The most common reason for discontinuation was TEAEs (20 participants).

Overall, for this interim CSR, 142 (90.4%) study participants completed Cycle 1 up to Day 43, 113 (93.4%) Cycle 2 up to Day 43, 83 (86.5%) Cycle 3 up to Day 43, 65 (92.9%) Cycle 4 up to Day 43, and 41 (78.8%) Cycle 5 up to Day 43. The number of study participants completing subsequent cycles up to Day 43 was low.

Figure 26: Study participant disposition



≈=equivalent dose; AE=adverse event; FAS=Full Analysis Set; N=number of study participants; SS=Safety Set Note: Dose modifications from ≈10mg/kg to ≈7mg/kg equivalent and vice versa are permitted at the beginning of the treatment cycles at the Investigator's discretion.
a The total number of study participants for each cycle was derived from the Day 43 visit. Cycle 6 is not the final cycle and participants may continue treatment.
b Other reasons included treatment with a prohibited treatment (plasma exchange) (N=1).
c Other reasons included treatment with a prohibited treatment (plasmapheresis) (N=1) and participant wanted to start a family (N=1).

The median age was 54.0 years and most patients were White (68.8%) and female (59.2%). The median time since diagnosis of gMG was 5.7 years, the median MG-ADL total score was 8.0, and the median QMG total score was 14.0. There were higher proportion of study participants from North America in the ≈7mg/kg group (26 [32.9%]) compared with the ≈10mg/kg group (18 [23.1%]) and the lower proportion of study participants from Europe in the ≈7mg/kg group (45 [57.0%]) compared with the ≈10mg/kg group (53 [67.9%]). The number of study participants in the <50kg body weight category was low in both the rozanolixizumab ≈7mg/kg group (4 [5.1%]) and ≈10mg/kg group (6 [7.7%]). The number of study participants who needed additional therapies in the observation period of MG0003 and entered MG0007, n (%), were 14 (17.7%) and 16 (20.5%) in the rozanolixizumab ≈7mg/kg and

≈10mg/kg groups, respectively. The 76.4% of patients were AChR-Ab seropositive and 5.7% were MuSK seropositive at MG0007 baseline. There were lower proportion of study participants who had undergone thymectomy in the rozanolixizumab ≈7mg/kg group (28 [35.4%]) compared with the ≈10mg/kg group (37 [47.4%]) and the higher proportion of study participants who were MuSK+ at MG0003 Baseline in the rozanolixizumab ≈7mg/kg group (8 [10.1%]) compared with the ≈10mg/kg group (2 [2.6%]).

During MG0007, 6 (7.6%) study participants in the rozanolixizumab ≈7mg/kg group and 8 (10.3%) in the rozanolixizumab ≈10mg/kg group received any rescue therapy (i.e., rescue medication or rescue procedure). Five (6.3%) study participants in the rozanolixizumab ≈7mg/kg group received rescue medication (4 received immunoglobulins [1 of which continued treatment with efgartigimod alfa] and 1 received methylprednisolone sodium succinate); 2 (2.5%) study participants required a rescue procedure (1 received plasma exchange and 1 received PEX). Seven (9.0%) study participants in the rozanolixizumab ≈10mg/kg group received rescue medication (6 received immunoglobulins [1 of which continued treatment with plasma, human albumin, and calcium chloride dihydrate/potassium chloride/sodium chloride/sodium lactate], 1 received methylprednisolone sodium succinate, and 1 received plasma [reported term: plasma exchange]]); 3 (3.8%) study participants required a rescue procedure (all required plasmapheresis). All study participants who received rescue therapies discontinued the study.

Table 58: MG-ADL score change from Baseline to Day 43 during each treatment cycle (Safety Set)

Treatment group	Statistic	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline
RLZ ≈7mg/kg (N=79)	n	79	73	54	50	41	35	31	29
	Mean	8.4	-3.6	7.9	-3.0	8.0	-3.4	7.6	-4.2
	SD	4.2	3.4	3.6	3.1	4.0	2.7	3.1	2.9
	Median	8.0	-3.0	7.0	-3.0	6.0	-3.0	7.0	-3.0
	Min, Max	0, 17	-14, 4	1, 19	-12, 5	2, 20	-10, 1	3, 14	-12, 1
RLZ ≈10mg/kg (N=78)	n	76	67	67	63	55	48	39	36
	Mean	8.0	-3.2	9.1	-3.8	9.0	-3.4	9.2	-3.3
	SD	4.0	3.2	4.0	3.9	3.0	3.3	3.5	3.2
	Median	8.0	-2.0	8.0	-3.0	9.0	-3.0	9.0	-3.0
	Min, Max	0, 18	-14, 2	2, 19	-15, 3	3, 15	-11, 4	1, 16	-12, 1

≈=equivalent dose; IMP=investigational medicinal product; max=maximum; MG-ADL=Myasthenia Gravis Activities of Daily Living; min=minimum; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SD=standard deviation Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (ie, Baseline [Day 1]) value for that cycle.
Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability

Observed results and changes from Baseline in the MG-ADL score by subgroup and study cycle were explored for subgroups of age, sex, region, weight, MG-specific autoantibodies, duration of disease at Baseline, MGFA disease class at Baseline, thymectomy at Baseline, and Baseline MG-ADL category.

Overall, a numerically smaller improvement in MG-ADL scores was observed at Day 43 among the elderly population (≥65 years) compared with the younger population (≥18 years to <65 years) in MG0007 (Cycle 1: –2.8 vs –3.6, Cycle 2: –2.0 vs –3.9, Cycle 3: –1.6 vs –3.9, Cycle 4: –2.2 vs –4.0, Cycle 5: –2.6 vs –4.7).

Overall, a trend towards a higher response in anti-MuSK+ study participants than in the overall population at Day 43 was observed for Cycle 1 (–5.1 vs –3.4) and Cycle 2 (–5.0 vs –3.5). The response was similar for Cycle 3 (–3.8 vs –3.4) and Cycle 4 (–3.0 vs –3.7). Conclusions should be drawn with caution due to the low number of participants in this subgroup (n≤8 per treatment group and cycle).

Overall, participants with a shorter duration of disease (<5.7 years) showed a better clinical improvement at Day 43 with repeated cyclic treatment (Cycle 1: −2.9, Cycle 2: −3.4, Cycle 3: −4.1, Cycle 4: −4.3, Cycle 5: −6.2) compared with participants with a longer duration of disease (≥5.7 years) (Cycle 1: −4.0, Cycle 2: −3.5, Cycle 3: −2.8, Cycle 4: −3.1, Cycle 5: −3.2).

Overall, participants with a Baseline MG-ADL category <5 showed a better clinical improvement at Day 43 with repeated cyclic treatment (Cycle 1: −0.9, Cycle 2: −2.9, Cycle 3: −5.4, Cycle 4: −8.5) compared with participants with a Baseline MG-ADL category ≥5 (Cycle 1: −4.0, Cycle 2: −3.5, Cycle 3: −3.2, Cycle 4: −3.4). Conclusions should be drawn with caution due to the low number of participants in the <5 subgroup after Cycle 3 (n≤7 per cycle). Following treatment, the absolute MG-ADL values in the <5 subgroup remained consistently lower compared with the ≥5 subgroup.

The interpretation of results is limited due to the low number of study participants in the following subgroups: age ≥85 years (≤1 study participant per treatment group and cycle), Asia excluding Japan (≤2), Japan (≤6), body weight <50kg (≤6), and MGFA Disease Class at MG0003 Baseline: Class IVa (≤3).

Table 59: MG-C total score change from Baseline to Day 43 during each treatment cycle (Safety Set)

Treatment group	Statistic	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline
RLZ ≈7mg/kg (N=79)	n	79	72	54	50	40	35	31	29
	Mean	15.4	-7.3	14.7	-6.1	15.4	-7.0	14.1	-7.4
	SD	7.6	6.8	6.6	5.5	8.0	5.6	6.1	6.7
	Median	15.0	-6.5	13.0	-7.0	15.0	-7.0	14.0	-6.0
	Min, Max	2, 34	-28, 11	1, 34	-15, 7	5, 42	-24, 2	5, 29	-27, 5
RLZ ≈10mg/kg (N=78)	n	75	67	67	63	55	47	39	35
	Mean	14.5	-5.1	16.9	-7.4	17.5	-6.5	17.3	-5.6
	SD	7.4	6.5	6.9	7.1	6.9	7.2	8.0	7.6
	Median	13.0	-3.0	16.0	-6.0	16.0	-6.0	17.0	-4.0
	Min, Max	0, 36	-30, 3	5, 34	-26, 5	4, 34	-28, 6	2, 36	-24, 6

≈=equivalent dose; IMP=investigational medicinal product; max=maximum; MG-C=Myasthenia Gravis Composite; min=minimum; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SD=standard deviation Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (ie, Baseline [Day 1]) value for that cycle. Note: MG-C scores range from 0 to 50, with a higher score indicating more severe disease

Table 60: QMG total score change from Baseline to Day 43 during each treatment cycle (Safety Set)

Treatment group	Statistic	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline	Baseline Observed Result	Change from Baseline
RLZ ≈7mg/kg (N=79)	n	79	72	54	49	40	35	31	29
	Mean	14.4	-4.4	14.7	-4.1	14.8	-5.1	15.0	-5.9
	SD	5.1	4.8	4.5	4.2	6.2	4.7	5.3	5.9
	Median	14.0	-3.5	14.0	-3.0	14.5	-4.0	16.0	-5.0
	Min, Max	3, 24	-18, 7	6, 27	-16, 3	3, 39	-19, 2	4, 25	-17, 4
RLZ ≈10mg/kg (N=78)	n	75	65	67	62	55	48	39	36
	Mean	15.3	-4.3	16.2	-4.8	16.5	-4.5	16.4	-4.3
	SD	4.7	4.5	5.2	5.6	4.8	4.6	6.3	5.3
	Median	15.0	-4.0	16.0	-4.0	16.0	-4.0	15.0	-3.0
	Min, Max	2, 25	-17, 5	4, 30	-25, 6	4, 29	-17, 3	2, 31	-19, 5

≈=equivalent dose; IMP=investigational medicinal product; max=maximum; min=minimum; n=number of study participants; N=total number of study participants in treatment group; QMG=Quantitative Myasthenia Gravis; RLZ=rozanolixizumab; SD=standard deviation
Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (ie, Baseline [Day 1]) value for that cycle. Note: QMG scores range from 0 to 39 with a higher score indicating more severe disability.

Table 61: Observed MG-ADL responder rates at Day 43 during each treatment cycle (Safety Set)

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
Treatment group	**n**	**Responders n (%)**	**n**	**Responders n (%)**	**n**	**Responders n (%)**	**n**	**Responders n (%)**
RLZ ≈7mg/kg (N=79)	73	54 (74.0)	50	33 (66.0)	35	27 (77.1)	29	25 (86.2)
RLZ ≈10mg/kg (N=78)	67	43 (64.2)	63	43 (68.3)	48	33 (68.8)	36	22 (61.1)
RLZ Total (N=157)	140	97 (69.3)	113	76 (67.3)	83	60 (72.3)	65	47 (72.3)

≈=equivalent dose; MG-ADL=myasthenia gravis Activities of Daily Living; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab.
Note: Percentages were based on the number of study participants with nonmissing data at each visit in the Safety Set.
Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability. Note: MG-ADL responder at a visit was defined as having at least 2-point improvement (decrease) from Baseline.
Note: Study participants were grouped according to the actual dose level received within the study cycle.

The estimated (Kaplan-Meier analysis) time to MG-ADL response was 15 days for the majority of cycles. Of note, a difference in time to response was observed in the first cycle between the 2 treatment groups (10 days for the ≈7mg/kg treatment group vs 23 days for the ≈10mg/kg treatment group).

Table 62: Time to MG-ADL response during each treatment cycle (Safety Set)

Treatment group	**Statistic**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**
RLZ ≈7mg/kg (N=79)	n	79	54	41	31
	Median (days)	10.00	15.00	15.00	9.00
	95% CI	8.00, 15.00	9.00, 17.00	9.00, 15.00	8.00, 15.00
	% Censored	16.46	24.07	9.76	9.68
RLZ ≈10mg/kg (N=78)	n	78	67	55	39
	Median (days)	23.00	15.00	14.00	14.00
	95% CI	15.00, 41.00	9.00, 22.00	8.00, 16.00	9.00, 27.00
	% Censored	33.77	16.42	20.00	28.21
RLZ Total (N=157)	n	157	121	96	70
	Median (days)	15.00	15.00	15.00	12.00
	95% CI	14.00, 19.00	10.00, 16.00	9.00, 15.00	9.00, 15.00
	% Censored	25.00	19.83	15.63	20.00

≈=equivalent dose; CI=confidence interval; MG-ADL=myasthenia gravis Activities of Daily Living; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab. Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: 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.
Note: Study participants who used rescue therapy within study cycle or who were withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response within study cycle were censored at time of event. Study participants who never achieved a response within study cycle were censored at the date of their last MG-ADL assessment.

Note: Survival estimate was calculated from Kaplan-Meier analysis.

The treatment-free interval (ie, time between the last infusion of the previous cycle to the first infusion of the next cycle) between the first 2 cycles was ~9 weeks in both rozanolixizumab treatment groups and ~7 to 8 weeks between Cycle 2 and Cycle 3. For a subset of participants with a higher frequency of treatment cycles, shorter treatment-free intervals of ~5 weeks were observed.

Table 63: Survival analysis of treatment-free interval (Safety Set)

Treatment group	Statistic	Between Cycle 1 and 2	Between Cycle 2 and 3	Between Cycle 3 and 4	Between Cycle 4 and 5
RLZ ≈7mg/kg (N=79)	n	79	54	41	31
	Median (days)	64.0	57.0	37.0	35.0
	95% CI	50.0, 86.0	43.0, 67.0	35.0, 50.0	30.0, 47.0
	% Censored	22.8	20.4	29.3	25.8
RLZ ≈10mg/kg (N=78)	n	78	67	55	39
	Median (days)	64.0	46.0	38.0	36.0
	95% CI	43.0, 99.0	37.0, 62.0	36.0, 43.0	31.0, 37.0
	% Censored	23.1	20.9	25.5	25.6
RLZ Total (N=157)	n	157	121	96	70
	Median (days)	64.0	50.0	38.0	36.0
	95% CI	51.0, 80.0	43.0, 64.0	36.0, 43.0	32.0, 37.0
	% Censored	22.9	20.7	27.1	25.7

≈=equivalent dose; CI=confidence interval; N=total number of study participants in treatment group; RLZ=rozanolixizumab. Note: Study participants were grouped according to the actual dose level received in the preceding study cycle.
Note: Study participants who did not commence a subsequent cycle were censored at the date of their last assessment within the study cycle.

Subgroup analyses performed by administered fixed dose for selected efficacy variables showed similar improvement in MG-ADL, MG-C, and QMG scores at Day 43 of the first 3 cycles for the 420mg, 560mg, 840mg, and 1120mg doses. A lower response was observed for the 280mg dose. ≤4 study participants received the 280mg dose and all other doses were administered to ≥15 study participants in the first 3 cycles.

For the proposed 2-fixed doses of 420mg (<50kg) and 560mg (≥50kg to <100kg), responder rates for MG-ADL, MG-C and QMC were consistent with those for the weight-tiered doses in the first 5 cycles (Table 68). In addition, the 560mg dose showed high responder rates across the ≥50kg to <70kg and ≥70kg to <100kg weight groups (>60% in the first 3 cycles, n>30).

Table 64: Overview of the change from baseline at Day 43 and responder rates in MG0007 by administered fixed dose for MG-ADL, MG-C and QMG (Observed data, SS)

	Changes from Baseline at Day 43								Responder at Day 43			
	Fixed dose				Weight-tiered RLZ dose				Fixed dose		Weight-tiered RLZ dose	
	420mg		560mg		≈7mg/kg		≈10mg/kg		420mg	560mg	≈7mg/kg	≈10mg/kg
Category	<50kg		≥50 to <100kg		All weights		All weights		<50kg	≥50 to <100kg	All weights	All weights
Cycle 1												
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
MG-ADL	6	-3.5 (2.4)	53	-3.5 (3.7)	73	-3.6 (3.4)	67	-3.2 (3.2)	5/6 (83.3)	34/53 (64.2)	54/73 (74.0)	43/67 (64.2)
MG-C	6	-5.0 (2.9)	53	-7.4 (7.5)	72	-7.3 (6.8)	67	-5.1 (6.5)	5/6 (83.3)	35/53 (66.0)	52/72 (72.2)	37/67 (55.2)
QMG	6	-5.2 (3.1)	52	-4.4 (4.8)	72	-4.4 (4.8)	65	-4.3 (4.5)	5/6 (83.3)	32/52 (61.5)	43/72 (59.7)	41/65 (63.1)

	Changes from Baseline at Day 43								Responder at Day 43			
	Fixed dose				Weight-tiered RLZ dose				Fixed dose		Weight-tiered RLZ dose	
	420mg		560mg		≈7mg/kg		≈10mg/kg		420mg	560mg	≈7mg/kg	≈10mg/kg
Category	<50kg		≥50 to <100kg		All weights		All weights		<50kg	≥50 to <100kg	All weights	All weights
Cycle 2												
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
MG-ADL	5	-1.2 (1.6)	43	-3.6 (3.6)	50	-3.0 (3.1)	63	-3.8 (3.9)	3/5 (60.0)	27/43 (62.8)	33/50 (66.0)	43/63 (68.3)
MG-C	5	-5.2 (6.2)	43	-6.5 (6.5)	50	-6.1 (5.5)	63	-7.4 (7.1)	4/5 (80.0)	33/43 (76.7)	37/50 (74.0)	51/63 (81.0)
QMG	5	-3.4 (4.0)	41	-5.0 (4.3)	49	-4.1 (4.2)	62	-4.8 (5.6)	2/5 (40.0)	27/41 (65.9)	29/49 (59.2)	40/62 (64.5)
Cycle 3												
	N	mean (SD)	N	mean (SD)	N	mean (SD)	n	mean (SD)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
MG-ADL	3	-2.7 (-)	32	-3.6 (3.1)	35	-3.4 (2.7)	48	-3.4 (3.3)	3/3(100.0)	23/32 (71.9)	27/35 (77.1)	33/48 (68.8)
MG-C	3	-10.3 (-)	32	-6.7 (5.4)	35	-7.0 (5.6)	48	-6.5 (7.2)	3/3 (100.0)	26/32 (81.3)	37/35 (77.1)	33/47 (70.2)
QMG	3	-4.0 (-)	32	-5.1 (4.7)	35	-5.1 (4.7)	48	-4.5 (4.6)	2/3 (66.7)	23/32 (71.9)	35/25 (71.4)	28/48 (58.3)
Cycle 4												
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
MG-ADL	1	-	29	-3.5 (3.2)	29	-4.2 (2.9)	36	-3.3 (3.2)	1/1 (100.0)	21/29 (72.4)	25/29 (86.2)	22/36 (61.1)
MG-C	1	-	28	-5.1 (5.1)	29	-7.4 (6.7)	35	-5.6 (7.6)	1/1 (100.0)	15/28 (53.6)	22/29 (75.9)	19/35 (54.3)
QMG	1	-	29	-4.6 (5.4)	29	-5.9 (5.9)	36	-4.3 (5.3)	0	17/29 (58.6)	18/29 (62.1)	21/36 (58.3)
Cycle 5												
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
MG-ADL	1	-	20	-4.7 (4.0)	16	-3.3 (3.4)	25	-4.9 (4.0)	1/1 (100.0)	17/20 (85.0)	12/16 (75.0)	20/25 (80.0)
MG-C	1	-	19	-8.1 (7.9)	16	-5.7 (6.8)	24	-8.4 (8.3)	1/1 (100.0)	15/19 (78.9)	10/16 (62.5)	19/24 (79.2)
QMG	1	-	20	-6.4 (4.3)	16	-4.3 (4.7)	25	-6.4 (5.6)	0	17/20 (85.0)	11/16 (68.8)	19/25 (76.0)

≈: approximate dose; MG-ADL: Myasthenia gravis activities of daily living; MG-C: Myasthenia Gravis Composite; QMG: Quantitative Myasthenia Gravis; RLZ: Rozanolixizumab.
Notes: Analyses were conducted in the safety set.
Percentages are based on the number of participants with non-missing data at each visit in the safety set.
Participants are grouped according to the actual dose level received within the study cycle.

MG0004

Study MG0004 enrolled 71 patients (among which 12 have received placebo in MG0003) for up to 60 weeks to evaluate the safety and efficacy of weekly rozanolixizumab treatment of up to 52 weeks followed by an observation period of 8 weeks. Patients were randomised to receive rozanolixizumab ≈7 mg/kg (n=35) or ≈10 mg/kg(n=36); all but one received at least 1 dose of treatment. Primary objectives were to evaluate the long-term safety and tolerability, and secondary objectives were to evaluate efficacy of up to 52 weeks of weekly administered rozanolixizumab.

Once MG0007 study was initiated, MG0004 enrolment closed (the number of study participants in MG0004 decreased steadily after Week 22), and ongoing MG0004 patients after a minimum of 6 visits were eligible to enter MG0007. Eight (11.3%) study participants completed the study. The majority of participants permanently discontinued the study, principally to transition to the MG0007 study (n=53, 74.6%). Three (4.2%) participants permanently discontinued the study due to TEAEs while 2 (2.8%) participants withdrew from the study.

The population enrolled in the study was representative of a gMG patient population with moderate to severe disease: at MG0004 Baseline, the mean (SD) MG-ADL score was 8.4 (3.6), the mean (SD) MG-C score was 15.4 (7.3), and the mean (SD) QMG score was 15.3 (5.3). In addition, >80% of study participants were anti-AChR+ and ~10% were anti-MuSK+ (assessed at MG0003 Baseline).

In both treatment groups, >75% of study participants had an exposure ≥3 months and approximately one third had an exposure ≥6months. Study participants in MG0004 were allowed to switch treatment groups for tolerability and efficacy reasons at the discretion of the Investigator. Efficacy analyses in MG0004 were conducted by first administered dose (ie, study participants as randomised).

Improvements (reduction from Baseline) were observed for MG-ADL, MG-C and QMG in both rozanolixizumab treatment groups with a consistent trend observed up to Week 33 (beyond that timepoint the number of study participants that continued in the study was ≤10 per treatment group at any scheduled timepoint). Overall, the mean reduction from Baseline up to Week 33 ranged between:

•MG-ADL: across visits during rozanolixizumab treatment, the mean decrease from Baseline for rozanolixizumab overall ranged between -2.9 and -3.6 in MG0004 (up to Week 33)

• MG-C: across visits during rozanolixizumab treatment, the mean decrease from Baseline for rozanolixizumab overall ranged between -5.0 and -7.4 in MG0004 (up to Week 33) compared with -2.9 and -6.6 in MG0003.

• QMG: across visits during rozanolixizumab treatment, the mean decrease from Baseline for rozanolixizumab overall ranged between -3.7 and -5.6 in MG0004 (up to Week 33) compared with -2.3 and -4.9 in MG0003.

Table 65: MG-ADL total score observed results and changes from baseline over time (Safety Set)

Treatment Period/Visit	Observed Result						Change from Baseline Result					
	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
RLZ ≈7mg/kg (N=35)												
Baseline	35	8.4	3.6	8.0	2	17	-	-	-	-	-	-
Treatment/Week 5	34	5.6	3.9	5.0	0	15	34	-2.7	3.3	-2.0	-13	2
Treatment/Week 7	35	5.6	3.7	6.0	0	12	35	-2.7	3.8	-2.0	-13	7
Treatment/Week 13	30	5.5	4.1	5.0	0	15	30	-3.1	3.4	-2.0	-12	2
Treatment/Week 25	18	4.7	3.2	4.5	0	11	18	-2.7	3.0	-2.0	-10	2
Treatment/Week 29	13	4.1	1.7	4.0	1	6	13	-2.8	2.1	-2.0	-6	0
Treatment/Week 33	10	3.7	2.2	4.0	0	7	10	-3.0	2.8	-2.0	-10	0
Treatment/Week 37	7	2.4	1.7	2.0	1	6	7	-3.9	2.5	-4.0	-7	0
Treatment/Week 52	5	3.2	1.5	3.0	1	5	5	-2.6	1.3	-2.0	-4	-1
Observation/Week 60	7	5.7	3.0	5.0	1	9	7	-0.3	2.1	-1.0	-3	3
RLZ ≈10mg/kg (N=35)												
Baseline	35	8.5	3.7	8.0	2	16	-	-	-	-	-	-
Treatment/Week 5	34	5.4	3.7	5.0	0	13	34	-3.2	3.8	-2.0	-12	4
Treatment/Week 7	32	4.8	3.2	4.5	0	13	32	-3.7	3.4	-2.0	-12	1
Treatment/Week 13	30	4.2	3.2	3.0	0	14	30	-3.9	4.0	-2.5	-12	1
Treatment/Week 25	17	3.7	3.7	2.0	0	14	17	-3.7	4.7	-2.0	-14	2
Treatment/Week 29	14	3.9	3.8	3.0	0	14	14	-3.6	4.3	-2.0	-13	1
Treatment/Week 33	12	3.9	3.6	3.5	0	13	12	-3.5	4.5	-2.5	-15	1
Treatment/Week 37	10	2.6	2.0	2.5	0	6	10	-3.6	3.6	-2.5	-13	0
Treatment/Week 52	3	2.3	-	3.0	0	4	3	-2.0	-	-3.0	-3	0
Observation/Week 60	7	6.0	3.2	5.0	1	10	7	-1.3	3.9	-3.0	-6	5

≈=equivalent dose; IMP=investigational medicinal product; max=maximum; MG-ADL=Myasthenia Gravis Activities of Daily Living; min=minimum; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SD=standard deviation Note: Not all timepoints are shown. Note: Baseline was defined as the last available value before or on the same date of first administration of IMP in MG0004. Note: The total MG-ADL score ranges from 0 to 24 with a higher score indicating more severe disability

The use of rescue medication was low (total of 4 [5.7%] study participants overall, only 2 of them while receiving rozanolixizumab).

The subgroup of anti-AChR+ study participants showed a trend in MG-ADL, MG-C and QMG score change from Baseline similar to the overall population. This improvement in clinical scales was associated with a decrease in the percentage change from Baseline in total serum IgG and AChR autoantibody levels.

For study participants who worsened before entering in MG0004, the majority were MG-ADL, MG-C, and QMG responders up to Week 45.

Overall, 37 (53.6%) study participants developed ADA against rozanolixizumab, and approximately half of them (18 [26.1%]) developed ADA that were neutralizing. For most study participants, the first occurrence of TE-ADA positivity was at Week 5 (14 [20.3%] study participants overall) or Week 9 (6 [9.8%]); only 7 study participants were TE-ADA positive for the first time at a later timepoint. The increase in the incidence of ADA positivity in study participants who restarted rozanolixizumab compared with those who were previously treated with placebo (46.2% vs 38.1%), in combination with the overall higher incidence of ADA positivity in MG0004 compared with MG0003 (53.6% vs 37.2%), suggest an increase in immunogenicity upon reinitiation of rozanolixizumab treatment.

Retreatment

Analyses were conducted to explore the treatment-free interval corresponding to the time between the last infusion of rozanolixizumab treatment to the first infusion of the next symptom-driven cycle. Irrespective of the treatment cycle, the majority of study participants had treatment-free intervals between 4 and 13 weeks. The estimated median for the first treatment-free interval was approximately 9 weeks and remained unchanged for the next interval. For the subset of patients with a higher frequency of treatment cycles, shorter treatment-free intervals of 5 to 7 weeks were observed. From cycle to cycle around 10 % of the study participants had a treatment-free interval shorter than 4 weeks.

In the pool of placebo-controlled study MG0003 and long-term extension study MG0007 data, after one treatment cycle of 6 rozanolixizumab weekly doses, 27.1 % (42/155) of patients developed ADA and 10.3 % (16/155) had antibodies that were classified as NAb. Upon reinitiating therapy, the proportion of patients who developed ADA and NAb increased to 65.0 % (13/20) and 50.0 % (10/20) after 5 treatment cycles. There was a small, non-clinically relevant effect of ADA on PK and PD, and no impact on efficacy and safety.

2.6.6. Discussion on clinical efficacy

Rozanolixizumab (Rystiggo) is being developed as an inhibitor of the FcRn activity with the aim to reduce the concentration of (pathogenic) IgG in patients with IgG autoantibody-mediated diseases.

There were two SAD studies submitted in the clinical development programme. The FIH study in healthy participants receiving iv or SC rozanolixizumab (UP0018), provided evidence that the SC route is the appropriate route of administration for multiple dosing of rozanolixizumab up to 7mg/kg for future clinical studies. Planned dose escalation to higher doses (14mg/kg and 25mg/kg) was not performed based on the safety and tolerability profile observed at the 7mg/kg iv dose. UP0060 investigated addition of 10 mg/kg SC dosing to 4 and 7 mg/kg doses and Japanese, Chinese, Caucasian population (healthy volunteers). Dose-dependent reductions in IgG and IgG subclasses were observed, and tolerability profile of 10 mg/kg was slightly worse. UP0106, another completed SAD study testing 280 and 560 mg SC doses in healthy volunteers aimed at investigating different administration methods.

Moderate to severe gMG was further studied in a phase 2 study (MG0002) and a phase 3 study (MG0003). MG0002 was a multicentre, randomised, double-blind, placebo-controlled, treatment sequence study

evaluating the safety, tolerability, and efficacy of two dose levels of rozanolixizumab (4mg/kg and 7mg/kg) in study participants with moderate to severe gMG. During MG0002, participants were treated with 3 weekly doses of either rozanolixizumab 7mg/kg or placebo, followed by 3 weekly doses of either rozanolixizumab 7mg/kg or 4mg/kg. Due to different treatment schedule and dosing (3+3) results from this study are only considered as proof of concept for efficacy and safety profile of 7mg/kg dose.

The evaluation of efficacy is primarily based on the single pivotal, placebo-controlled Phase 3 study (MG0003) in moderate to severe gMG with four flat SC dosing regimens in ≈7mg/kg (280mg, 420mg, 560mg and 840mg) and ≈10mg/kg treatment arms (420mg, 560mg, 840mg and 1120mg), based on four weight tiers (≥35kg to<50kg, ≥50kg to <70kg, ≥70kg to <100kg and ≥100kg), for one treatment cycle of 6 weeks, followed by an observation period of 8 weeks. The ≈7mg/kg dose was selected to replicate and confirm clinical improvements in MG-ADL achieved in MG0002, and the ≈10mg/kg dose was introduced to assess if additional benefit could be gained through either a greater magnitude of effect or shorter time to onset of clinical response, while maintaining a positive benefit-risk profile. The dosing in Phase 3 study was not endorsed by a CHMP scientific advice and several concerns on proposed dosing strategy were shared with the applicant.

Study MG0003 does not address sustained efficacy beyond the first cycle or after frequent re-administration. Additional data from the interim cutoff of the ongoing Phase 3 OLE study (MG0007, repeated cyclic treatment as clinically needed) as well as the completed Phase 3 OLE study (MG0004, chronic treatment) provided evidence to support the safety and efficacy evaluation for rozanolixizumab beyond first treatment cycle. Chronic administration concept for gMG (evaluated in the MG0004 OLE study), was discontinued after a minimum of 6 cycles were completed per participant, and at the initiation of MG0007, ongoing MG0004 participants were eligible to enter MG0007. From a clinical point of view, on-demand treatment strategy is supported over chronic treatment strategy. With respect to efficacy this concerns potential loss of efficacy in the treatment free intervals or increased risk of ADA upon re-exposure in the on-demand study arm in contrast to the continuous treatment arm. Although not recommended, chronic treatment with IVIG or PLEX had been used by clinicians as one of last resources and they are knowledgeable about managing cyclic treatments in gMG patients. There are also other FcRn targeting therapies either approved or in development for treatment of gMG patients. Additionally, for safety, pauses within treatment cycles may allow for (partial) IgG regeneration which may reduce the risk for critical decreases in IgG and serious infections. However, blinding would have strengthened the validity of the results beyond the first cycle and use of two doses in OLE studies is not supported, per CHMP comments during SA in 2019.

For labelling, a 2-fixed dosing regimen of rozanolixizumab was initially proposed in gMG patients: 560mg for patients weighing ≥50kg and 420mg for patients weighing ≥35 to <50kg. The applicant has been changing the dosing strategy continuously during the clinical development programme, progressing from weight-based dosing in phase 2 study MG0002 to weight-tiered dosing in the gMG phase 3 study, with a fixed dose in each of the 4 tiers testing a dose-span of 5.6 mg/kg – 8.4 mg/kg or 8.4 - 12.0 mg/kg, and now suggesting only 2 fixed doses for use in clinic. This is supported partially by clinical data (up to 100 kg) and partially by modelling (above 100 kg). However, the addition of the 10 mg/kg dose tier in the phase III pivotal trial without a valid scientific reason or previous data in gMG to support the additional dose is not understood. Suggestion of flat dosing equivalent to a weight-tiered dosing of ≈10mg/kg for participants weighing ≥35 to <50kg, and 50 to <70kg while suggestion of ≈7mg/kg equivalent for participants weighing 70 to <100kg was not entirely understood and questioned due to minimal change in the efficacy profile and noticeable changes in the safety profile. Suggestion of 560 mg dose for patients above 100kg with no clinical efficacy data in gMG was a major concern. In response to the major concern on dosing, the applicant suggested to use the doses coming from the 7 mg/kg weight tiered dosing. This was agreed. Additionally, use of medical devices for SC infusion and home-administration recommendation without any related data or discussion were concerns which were solved.

Design and conduct of clinical studies

MG0003

The design of the pivotal trial is a multicentre, multinational, randomised, double-blind, placebo-controlled, 3-arm confirmatory trial. The study consisted of screening (up to 28 days to account for central laboratory testing turn-around time), 6 weeks treatment, and 8 weeks blinded observation periods (began a week after the last infusion). Rescue therapy (IVIG and PEX) resulted in discontinuation of rozanolixizumab therapy. The maximum duration of the study per study participant was up to 18 weeks. The study was overseen by an IDMC, and a central laboratory was used for confirmation/detection of AChR-Ab and MuSK-Ab serotypes. The overall study design is considered acceptable but dose finding in phase III, the length of follow up and lack of double-blinded data on re-treatment are important limitation, and treatment details and enrolled population will be discussed further.

Eligible subjects were randomised in a 1:1:1 ratio to receive either one of SC abdominal infusion of weight-tiered flat dosing regimens equivalent to ≈7mg/kg and ≈10mg/kg rozanolixizumab or placebo in addition to their ongoing and stable treatment for gMG. Subjects were stratified according to AChR-Ab or MuSK-Ab status. No stratification was done for background gMG therapy (defined as corticosteroids, immunosuppressants and parasympathomimetics) or region, but baseline MG-ADL score, region, and stratification factors were used as covariates for adjustment of primary analysis.

The inclusion criteria are specific for gMG limiting the population to symptomatic patients with confirmed diagnosis, and together with exclusion criteria can generally be considered suitable to define a relevant patient population.

Eligible subjects were males or females, aged 18 years or older, with confirmed diagnosis of MG (based on medical history and previous evaluations) and symptomatic generalised MG (who are defined as patients with MG-ADL total score of ≥3 points at screening and baseline with ≥3 points attributed to non-ocular symptoms and QMG score of ≥ 11, but not in manifest myasthenic crisis, impending crisis, or severe weakness of oropharyngeal or respiratory muscles) with confirmed positive record of autoantibodies against AChR or MuSK. Patients who might need urgent care should not be treated with rozanolixizumab as onset of response could be delayed or drug interactions might jeopardise their emergency care and this information has been added to the SmPC.

Nine patients (newly diagnosed and untreated patients) were enrolled without background therapy but was considered for treatment such as IVIg or PEX by the Investigator. Previously treated patients with suboptimal response were enrolled and they continued to receive concomitant gMG therapies (oral corticosteroids; immunosuppressants such as methotrexate, mycophenolate mofetil, cyclosporine, azathioprine, tacrolimus; cholinesterase inhibitors) if they met "stable" definitions before screening and throughout the trial. However, no stratification on the concomitant gMG medication was carried out at the randomisation.

Patients were excluded if they had received immunosuppressants (, biologics, or others within defined periods prior to baseline visit, or undergone thymectomy within 6 months, or had thymoma which required chemotherapy or radiotherapy at any time. The conduction of a placebo-controlled trial despite available approved therapies can be criticised, however, it is acceptable as selected immunosuppressants and steroids were allowed as background therapies, and rescue therapy was allowed.

As rozanolixizumab interferes with the FcRn recycling mechanism of IgG, the serum concentrations of IgG-based medicinal products (e.g., mAb and IVIg) and Fc–peptide fusion proteins are expected to be decreased if administered concomitantly. It is recommended to initiate these treatments 2 weeks after administration of rozanolixizumab and to monitor for attenuated efficacy of these medicinal products when administered concomitantly. Use of IV or SC immunoglobulins, plasma exchange,

immunoadsorption, and plasmapheresis may reduce circulating levels of rozanolixizumab and is reflected in the SmPC. Also potential nonresponder groups was discussed (e.g. patients with documented lack of clinical response to PLEX or who require rescue therapy at the initiation of therapy or during the treatment cycle) and the success or failure of any gMG treatment depends on different factors including, but not limited to the individual clinical situation, extrinsic factors impacting disease exacerbation, concomitant treatment with medications that may worsen MG, genetic factors, and treatment compliance. At present it is unknown whether there are specific predictors for response to treatment with rozanolixizumab in gMG.

Only contraindication is hypersensitivity to the active substance or excipients. Known hypersensitivity to other FcRn targeting is not a contraindication**.** Rozanolixizumab contains proline and could be harmful for patients with hyperprolinaemia. The SmPC includes this information as a warning in section 4.4 of the SmPC.

Other main restrictions through the exclusion criteria addressed immunodeficiency, infections and malignancy risk. Patients were not permitted to enrol in the study if they had a serum total IgG level ≤5.5g/L or an absolute neutrophil count <1500 cells/mm3. Additionally, patients with IgG levels falling below 1g/L temporarily discontinued therapy. Patients with any clinically relevant active infection or serious infection, tuberculosis (current, at high risk, latent tuberculosis, nontuberculous mycobacterial infection), active hepatitis B infection, hepatitis C or HIV seropositivity, and patients who had a history of malignancy, including malignant thymoma, or patients with a current or medical history of primary immunodeficiency or IgA deficiency, splenectomy, transplant history were excluded from the pivotal study and were not studied with rozanolixizumab. Laboratory exclusion criteria were detailed and patients with severe renal impairment, hepatic disorders or ECG issues were not allowed in the study.

A total of 200 patients were randomised to flat dose tiers equivalent to rozanolixizumab ≈7mg/kg (n=66) and rozanolixizumab ≈10mg/kg (n=67) or placebo (n=67) on top of their background therapy at 81 potential international sites (actual recruitment in 15 countries). Autoantibody status was AChR-Ab seropositive in 179 (89.5%) patients (randomised set) and MuSK-Ab seropositive in 21 (10.5%) patients. Central laboratory results were AChR-Ab seropositive in 165 (82.5%) patients and MuSK-Ab seropositive in 16 (8%) patients. In total 60% (n=120) of the population was enrolled and 79 participants were treated with rozanolixizumab in Europe region, and 55 of these participants were enrolled in EU region. This is considered sufficient representation of EU for an orphan disease. At entry, most patients were concomitantly treated with anticholinesterases (86%), steroids (64.5%) and/or immunosuppressants (51.5%) and no changes were allowed during the study. There are no observable differences between efficacy in different subgroups according to background therapy. The most frequently reported MGFA class at screening was Class III in 114 (57%) patients followed by Class II in 78 (39%) patients, indicative of a symptomatic patient population with mainly moderate to mild weakness affecting muscles other than the ocular muscles. This is milder than the intended moderate to severe population despite MG-ADL and QMG inclusion criteria. Still, the mean baseline MG-ADL (8.3) and QMG (15.6) scores demonstrate substantial disease burden despite ongoing gMG treatment. Extrapolation of efficacy to all gMG severity levels was justified. Overall, 128 (64%) patients completed the study and 52 (81.3%) patients in the rozanolixizumab ≈7mg/kg group, 48 (69.6%) in the ≈10mg/kg group, and 56 (83.6%) in the placebo group received all 6 infusions (excluding mock infusions). Most patients who discontinued from treatment rolled over to OLE studies as they needed rescue therapies during observation period (59 patients, 29.5% in total). There were more discontinuations due to AEs in the rozanolixizumab ≈10mg/kg group (5 [7.5%]) compared with the ≈7mg/kg (2 [3.0%]) and placebo (2 [3.0%]) groups, whereas there were more discontinuations due to lack of efficacy in the placebo group (5 [7.5%]) compared with the rozanolixizumab ≈10mg/kg (1 [1.5%]) and ≈7mg/kg (1 [1.5%]) groups. There were slight imbalances between treatment arms in terms of demographics and disease characteristics, most probably due to small number of patients overall for a three-arm study and stratification criteria on

autoantibody status. There were not many notable differences among the treatment groups which would be expected to favour treatment with rozanolixizumab, except for higher frequency of past myasthenic crisis in placebo group. Fewer participants in the <50kg body weight category with a lower proportion in the rozanolixizumab ≈10mg/kg group (1.5% vs 6.0% in placebo, 10.6% in rozanolixizumab ≈7mg/kg) is major limitation as high dose is proposed for low weight groups.

Chosen endpoints are considered acceptable in general but some concerns that were raised during the SA are important. The evaluation of efficacy was based mainly on MG-ADL scale (subjective assessment of MG symptoms by the patient) and supported by QMG scale (quantitative evaluation of relevant muscle groups by the physician), MGC scale (combining physician examination and patient reported outcomes) and MG symptoms PRO score (which was developed by the applicant). Absolute changes from baseline and responder definitions were used for primary, secondary or exploratory endpoints. Specifically, MG-ADL and QMG are validated standard methods for evaluation of MG and have been previously used in several clinical studies in this condition, so assessed as the main proof of efficacy. As informed during the SA, MG symptoms PRO scores are in their validation process hence can only be considered as exploratory. MG-QoL15r and MGII were also used as MG specific scales but not as primary or key secondary endpoints, they are considered as supportive at best.

MG-ADL responder is defined as the participant who had a reduction of ≥2 points from baseline on the MG-ADL score at Day 43. QMG responder is defined as the participant who had a reduction of ≥3 points from baseline on the QMG score at Day 43. These endpoints could have been defined better to exclude responses which were not sustained through consequent visits, however due to their exploratory nature they were not queried.

The study followed a 2-stage confirmatory group sequential design using a combination test based on the inverse-normal method of combining independent stagewise p-values applying equal weighting of each stage. The primary analysis was based on the RS using a hypothetical & treatment policy strategy for intercurrent events with missing MG-ADL scores handled under a MAR assumption. Additional analyses using different strategies for handling intercurrent events (hypothetical, treatment policy, or composite strategy) were applied. The analyses of the secondary endpoints followed the same approach. This is accepted.

A sequential hierarchical test procedure was applied for the primary and secondary efficacy endpoints to protect the overall significance level for the multiplicity of endpoints and treatment groups. This is accepted.

MG0004

Study MG0004 enrolled 71 patients (among which 12 have received placebo in MG0003) for up to 60 weeks to evaluate the safety and efficacy of weekly rozanolixizumab treatment of up to 52 weeks followed by an observation period of 8 weeks. Patients were randomised to receive rozanolixizumab ≈7 mg/kg (n=35) or ≈10 mg/kg(n=36); all but one received at least 1 dose of treatment.

Once MG0007 study was initiated, MG0004 enrolment closed (the number of study participants in MG0004 decreased steadily after Week 22), and ongoing MG0004 patients after a minimum of 6 visits were eligible to enter MG0007. Eight (11.3%) study participants completed the study. Most participants permanently discontinued the study, principally to transition to the MG0007 study (n=53, 74.6%). Three (4.2%) participants permanently discontinued the study due to TEAEs while 2 (2.8%) participants withdrew from the study.

MG0004 is an open label study with no placebo or active control, the treatment was administered as chronic weekly treatment, and the participants were allowed to switch treatment groups for tolerability and efficacy reasons at the discretion of the Investigator. For these reasons, secondary efficacy endpoints

are of very limited value and only contributes to pooled analyses with the data from the first cycle in this study.

MG0007

The ongoing study MG0007 enrolled 165 patients who rolled over from MG0003 (105) and MG0004 (60) studies (35 participants having received placebo in MG0003 rolled over directly to MG0007).

Each cycle consisted of 6 weeks of treatment followed by an observation period. Initiation of additional treatment cycles were based on clinical evaluation of gMG symptoms. Four weeks were to be maintained between cycles unless IgG levels returned to ≥ 2 g/L within the 4 weeks, then additional treatment cycles could be initiated earlier.

Respectively 88 (52 from MG0003 and 36 from MG0004) and 77 (53 from MG0003 and 24 from MG0004) study participants were assigned to the ≈7mg/kg and ≈10mg/kg rozanolixizumab treatment groups in cycle 1. At the time of data-cutoff for the interim CSR (08 Jul 2022), 157 study participants had received rozanolixizumab in their first MG0007 cycle (safety set); no participants had completed the study, most of them (n=123) were ongoing in the study and 34 had discontinued the study (21.7%). The most common reason for discontinuation was TEAEs (20 participants). During MG0007, 6 (7.6%) study participants in the rozanolixizumab ≈7mg/kg group and 8 (10.3%) in the rozanolixizumab ≈10mg/kg group received any rescue therapy.

Overall, 142 (90.4%) study participants completed Cycle 1 up to Day 43, 113 (93.4%) Cycle 2 up to Day 43, 83 (86.5%) Cycle 3 up to Day 43, 65 (92.9%) Cycle 4 up to Day 43, and 41 (78.8%) Cycle 5 up to Day 43. The number of study participants completing subsequent cycles up to Day 43 was low.

Pooled Analysis

To explore clinical response and the duration of treatment-free interval in gMG patients following repeated 6-week cyclic treatment with rozanolixizumab, data from MG0003 were pooled with the OLE studies, MG0007 and MG0004 (first 6 weeks).

Pool E1 (n=127): Study participants receiving ≥ 2 treatment cycles based on MG symptom worsening. Data from MG0003 + MG0007 + 1st 6 weeks of MG0004 & 1st cycle of MG0007 will be included if entered study due to the need for rescue in MG0003 Observation Period.

Pool E2 (n=167): Study participants who have received rozanolixizumab treatment and initiated or awaiting the first treatment cycle based on MG symptom worsening

Pool E3 (n=110): Study participants receiving ≥2 consecutive treatment cycles based on MG symptom worsening.

Efficacy analyses were performed on Pool E1 and sensitivity efficacy analyses were performed on Pool E3. Pool E3 is a subset of Pool E1 excluding participants who had fixed cycles or chronic treatment between symptom-driven cycles and allows for a sensitivity analysis of the data. The 6-week Treatment Period is regarded as one treatment cycle for the purpose of cyclic treatment analysis.

Kaplan Meier analyses were conducted in Pool E2 to explore the treatment-free interval (ie, the time between the last infusion of rozanolixizumab to the first infusion of the next symptom driven cycle).

Efficacy data and additional analyses

MG0003 / first cycle

MG0003 study met its primary endpoint, meaning symptomatic relief on MG-ADL as reported by patients (less functional disability of MG patients), during first treatment cycle (RS). At Day 43 (Visit 10), the

primary endpoint was statistically significant for both rozanolixizumab treatment groups. The differences in least square (LS) mean change from Baseline in MG-ADL score between groups (rozanolixizumab minus placebo) were -2.586 (95% CI: -4.091, -1.249; p<0.001) for ≈7mg/kg rozanolixizumab group, and -2.619 (95% CI: -3.994, -1.163; p<0.001) for ≈10mg/kg rozanolixizumab group. The absolute mean difference was 2 points for both treatment arms, which could be considered as clinically meaningful.

The sensitivity analyses of the primary hypothesis were in general supportive of the primary analysis which are important to address some potential concerns. Per protocol analysis was not performed for efficacy endpoints, due to applying the estimand framework. For primary analysis the intercurrent events such as discontinuations or rescue treatment were not handled as non-responders. The treatment compliance was also a factor to enquiry about. In the RS using study participants receiving all 6 doses of IMP, LS mean MG-ADL change from baseline to D43 were -2.011 (95% CI: -3.506, -0.558; p=0.003) for Rozanolixizumab ≈7mg/kg, -2.018 (95% CI: -3.554, -0.504; p=0.003) for Rozanolixizumab ≈10mg/kg. In the RS using the composite strategy where any intercurrent events were handled by evaluating the corresponding participants as treatment failures and imputed with a worst score: The differences in LS mean change from Baseline in MG-ADL score between groups (rozanolixizumab minus placebo) were -2.568 (97.5% CI: -3.929, -1.207; p<0.001) for ≈7mg/kg rozanolixizumab group, and -2.733 (97.5% CI: -4.101, -1.365; p<0.001) for ≈10mg/kg rozanolixizumab group. Absolute LS mean scores were -1.3, -3.9, -4.0 for placebo, ≈7mg/kg, ≈10mg/kg rozanolixizumab groups, respectively. These two sensitivity analyses are considered important support for the primary analysis.

Other sensitivity or supplementary analyses were also supportive: the FAS, the RS using the jump to reference approach for imputation of missing scores, the FAS but excluding confirmed COVID-19 cases, the RS using the Treatment Policy Strategy for handling intercurrent events, the RS to assess the impact of the COVID-19 pandemic, or the RS in an exploratory analysis using historical AChR and MuSK values as covariates instead of baseline values.

Secondary efficacy endpoints were part of the sequential testing procedure and were supportive of the primary analysis. It is noted that, all secondary endpoints have shown a dose dependent response except for MG Symptoms PRO -Bulbar Muscle. Similar to the MG Symptoms PRO -Bulbar Muscle score, primary endpoint did not show dose dependent response.

In secondary endpoints, QMG is considered important as a physician rated scale. For QMG, a 3.5-point difference has been shown to correlate with clinically meaningful change. The MID with mild to moderate MG (QMGS ≤16) was calculated to be 2 points, although patients with higher baseline values (QMGS >16) had a higher MID of 3 points, which is a well-described phenomenon. The result is considered as clinically significant (LS mean change of -3.483 (95% CI: -5.614, -1.584; p<0.001) from Baseline in favour of rozanolixizumab ≈7mg/kg doses, -4.756 (95% CI: -6.821, -2.859; p<0.001) in favour of rozanolixizumab ≈10mg/kg doses).

MGC has 10 items: 2 ocular (diplopia and ptosis) from the QMGS; 4 items (facial, neck, deltoids, and hip flexors strength) from the MMT (Manual Muscle Test), and 4 patient-reported items from the MG-ADL (chewing, swallowing, breathing, and speech). The MID for individuals was estimated at 3 points. LS mean change of -3.901 (95% CI: -6.634, -1.245; p<0.001) from Baseline in favour of rozanolixizumab ≈7mg/kg doses, and -5.525 (95% CI: -8.303, -2.968; p<0.001) in favour of ≈10mg/kg doses are clinically significant.

The proportion of MG-ADL responders at Day 43 using the Composite Strategy (≥2.0 points improvement from Baseline) were 68.2% (n=45) in ≈7mg/kg group and 61.2% (n=41) in ≈10mg/kg group in comparison to the 28.4% in placebo group (n=19). OR for ≈7mg/kg group was 5.765 (p<0.001).

Unfortunately, the suggested dosing in the originally proposed SmPC is not fully in line with the tested doses in phase III study, hence the primary and secondary endpoint analyses cannot be directly presented in the originally proposed SmPC as main proof of evidence. The applicant has presented an analysis of the phase III data (primary and selected secondary endpoints: absolute changes and responders according to MG-ADL, MG-C, QMG scales) representing the weight subgroups and participants who received the recommended doses per subgroup per originally proposed SmPC text. The data from the analysis of the suggested doses showed that the <50 kg subgroup did not demonstrate any benefit on mean improvement from baseline to D43 on any of the validated known scales including MG-ADL, QMG, MGC which shows that neither the patients nor the physicians could detect benefit in this subgroup with rozanolixizumab treatment (-1.3 mean improvement on MG-ADL in placebo and ≈7mg/kg rozanolixizumab groups). In fact QMG scores were showing that physicians found out that patients on placebo were doing significantly better in this subgroup (-3.3 improvement in placebo group and -1.9 in ≈7mg/kg rozanolixizumab group). MG-ADL responder rate was showing minimal benefit (25% responders in placebo group and 43% in ≈7mg/kg rozanolixizumab group) and this was not confirmed by counteracting QMG responder data from physicians (50% responders in placebo group and 43% in ≈7mg/kg rozanolixizumab group). As the numbers are very small it is difficult to reach any conclusions. The data also showed that the 4 patients out of 12 patients <50kg who have chosen to stay in therapy in the MG0007 study and received ≈7mg/kg rozanolixizumab, had clinically meaningful improvement in the first cycle (-3.3 points on MG-ADL) but this benefit went back to placebo levels of improvement (-1 or-1.3 points on MG-ADL) during further cyclic treatments. These data are showing that there are some selected patients <50kg benefiting from rozanolixizumab therapy but the numbers are too small to draw any conclusions. However, the applicant justified that based on the observed changes from Baseline in total IgG and anti-AChR autoantibodies of approximately 70% in MG0003, a 280mg dose of rozanolixizumab is expected to be effective for the treatment of gMG in study participants <50kg.

In the subgroup analyses for the primary endpoint, some subgroups demonstrated inconclusive results such as Asian (n=7), Japanese (n=13), <50kg weight (n=12) participants. For the flat doses, weight subgroup analyses of primary endpoint demonstrated no meaningful benefit observed with 10 mg/kg dose in <50 kg group (n=1) (-0.009 mean difference from placebo), -3.027 mean difference for 50-70 kg group with 10 mg/kg dose, -3.398 mean difference for 70-100 kg group with 7 mg/kg dose. For participants above 100 kg, the mean difference was numerically lower (-2.479) with 7 mg/kg dosing. Subgroup analyses for secondary endpoints are consistent with above observations.

MuSK-Ab seropositive subgroup was also small, and results differed significantly from AChR-Ab seropositive group. The improvement observed in historical or current AChR seropositive patients was marginal, and the LS mean difference for active arms versus placebo ranged between 1.9 to 2.6 points on MG-ADL scale. However, the small number of patients (4 to 8 participants per arm) in MuSK seropositive group have shown LS mean difference for active arms versus placebo ranging between 4.2 to 9.6 points on MG-ADL scale. In the historical MuSK seropositive subgroup, 1 study participant in the ≈10mg/kg group discontinued treatment after 7 days of exposure due to adverse event but was identified as responder at the premature end of treatment visit, and 1 study participant in the placebo group discontinued treatment after 22 days of exposure due to lack of efficacy. So, in conclusion, the number of MuSK-Ab seropositive participants may be too low in the pivotal trial to provide statistically compelling results and to claim external validity of results for this population. However, 21 patients in a randomised placebo-controlled trial, included in primary analysis population, and showing highly significant difference between placebo and active treatment groups is considered important due to very high unmet medical need and very limited treatment options in this population. The subgroup analysis of MG0003 reflect evidence regarding the efficacy of rozanolixizumab treatment in anti-MuSK+ subpopulation, which was maintained throughout repeated cyclic treatment. The PD data, showing lowering of IgG4 in line with total IgG is further supporting these clinical findings.

Results in region Europe were consistent with overall group. Subgroup analyses according to background gMG therapy were consistent with the primary analysis.

The median time to MG-ADL response favoured treatment arms versus placebo and low dose group seemed to have an earlier response tendency (16 days in the rozanolixizumab ≈7mg/kg group, 22 days in the ≈10mg/kg group). This is considered suitable with the IgG decline. A rapid mean decreases from Baseline in total serum IgG of 43.7% for the rozanolixizumab ≈7mg/kg group and of 51.7% for the rozanolixizumab ≈10mg/kg group was achieved at Day 8 (1 week following the first dose). The mean maximum reduction from Baseline in total serum IgG during the study (Treatment Period and Observation Period) was 71.1% for the rozanolixizumab ≈7mg/kg group and 77.7% for the rozanolixizumab ≈10mg/kg group.

According to mean changes from baseline in MG-ADL, QMG, and MG-C by administered dose in the Randomised Set, the effect seems to peak around day 36. Although the differences are not quite obvious in QMG and MG-C scales for 420-560-840-1120 mg administered dose groups, on MG-ADL scale 420 mg and 560 mg doses were slightly separating from all others. Additionally, 280 mg demonstrated lower efficacy than other doses. However, this was not supported by the total serum IgG changes per dose. Mean maximum percentage changes from Baseline for total serum IgG were generally similar across the administered dose range. The median maximum percentage change from Baseline was slightly lower for the 280mg dose compared with the higher doses; however, variability was high.

Achieving minimal symptom expression is important therapy goal for gMG. In this study it is defined as an MG-ADL total score of 0 or 1, at any time during the Treatment and Observation Periods. A higher proportion of study participants achieved minimal symptom expression at any time in both rozanolixizumab groups (17 [25.8%] study participants in the ≈7mg/kg group and 19 [28.4%] in the ≈10mg/kg group) compared with the placebo group (2 [3.0%]).

Pooled data / Symptom-driven cyclic therapy

To assess the efficacy of MG symptom-driven repeat 6-week cyclic treatment with rozanolixizumab, MG0007 data (cutoff 08 Jul 2022) and limited data from MG0004 (first 6 weeks) are integrated with MG0003 for the pooled analyses.

Study MG0003 only evaluated one treatment cycle and does not address sustained efficacy beyond the first cycle or after frequent re-administration (on demand).

The MG0007 study is ongoing and with the data included from study MG0004, 115 AChR-Ab seropositive patients (127 overall) received two consecutive symptom driven cycles, only 69 of them followed up to 4 cycles. The long-term efficacy should be investigated further.

As observed with the results from study MG0007, pooled analyses support the notion that treatment effect with the study MG003 seemed to be maintained over time in OLE; with well-known caveats of open label design and withdrawal bias. For the 280mg dose, a trend for a lower response was observed in MG0007.

In Pool E2, the estimated median treatment-free interval to the first symptom-driven cycle was ~9 weeks (ie, 63 days) for the overall population. The probability for participants to achieve treatment-free intervals of at least 15 weeks (105) days was >25%. For the participants with frequent treatment cycles, the treatment-free intervals remained stable over time (5 to 7 weeks). Irrespective of the treatment cycle, the majority of study participants had treatment-free intervals between 4 and 13 weeks. Of note, from cycle to cycle, ~10% of the study participants had a treatment-free interval <4 weeks.

2.6.7. Conclusions on the clinical efficacy

Overall, administered rozanolixizumab doses in comparison to placebo has demonstrated its efficacy at the end of the first treatment cycle in adult gMG population studied in study MG0003, as rated by patients and physicians.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

To date, the safety of rozanolixizumab has been investigated in 8 completed and 7 ongoing clinical studies across a range of indications and dosing regimens (Table 66). With the exception of the FIH study (UP0018) which also evaluated IV dosing, in all of the completed and ongoing clinical studies rozanolixizumab (and placebo) have been administered by SC infusion. Rozanolixizumab has been studied with body weight-normalised dosing (mg/kg) in Phase 1 studies (UP0018 and UP0060), Phase 2 studies in gMG (MG0002), ITP (TP0001), and CIDP (CIDP01 and CIDP04), and with a fixed-dose regimen in AIE001 and MOG001. The dosing of rozanolixizumab in MG0003, MG0004, and MG0007, was based on a weight-tiered approach with different fixed doses across 4 body weight tiers. Weight-tiered dosing was also used in the Phase 3 ITP studies (TP0003, TP0006, and TP0004).

Table 66: Overview of completed, ongoing and planned clinical studies.

Study number/ Region	Study objectives	Study design	Dose(s) (mg)	Number of participants	Mean age of study participants/ range
Completed					
MG0003/ Asia, Canada, Europe, and US	Evaluate efficacy and safety of rozanolixizumab in gMG	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Rozanolixizumab or placebo sc: Weight-tiered doses of ≈7mg/kg or ≈10mg/kg Q1W x6	200	51.8 years/18 to 89 years
MG0004/ Asia, Canada, Europe, and US	Evaluate long-term safety, tolerability, and efficacy of rozanolixizumab in gMG	Phase 3, multicenter, randomized, 2-arm, OLE study	Rozanolixizumab sc: Weight-tiered doses of ≈7mg/kg or ≈10mg/kg Q1W x52	70 study participants (study was replaced by MG0007)	52.2 years/19 to 89 years
MG0002/ Canada, Europe, and US	Evaluate efficacy, safety, and tolerability of rozanolixizumab in study participants with gMG	Phase 2a, multicenter, randomized, investigator-blind, participant-blind, placebo-controlled 2-arm, repeat dose, treatment sequence study	Dosing Group 1: Rozanolixizumab or placebo sc: 7mg/kg Q1W x3 Dosing Group 2: Rozanolixizumab sc: 7mg/kg Q1W x3 followed by 4mg/kg Q1W x3	43	51.9 years/ 25 to 81 years
TP0001/ Australia and Europe	Evaluate safety, efficacy, and tolerability of rozanolixizumab in study participants with primary ITP	Phase 2, multicenter, open-label, multiple-arm, multiple-dose study with escalating dose cohorts	Rozanolixizumab sc: 4mg/kg Q1W x5 7mg/kg Q1W x3 10mg/kg Q1W x2 15mg/kg single dose 20mg/kg single dose	66	50.8 years/ 20 to 86 years
CIDP01/ Canada, Europe, and US[a]	Evaluate safety, efficacy, and tolerability of rozanolixizumab in CIDP	Phase 2a, multicenter, randomized, investigator-blind, participant-blind, placebo-controlled, parallel-group study	Rozanolixizumab or placebo sc: 10mg/kg Q1W x12	34	56.8 years /23 to 77 years

CIDP04/ Canada, Europe, and US[a]	Evaluate long-term safety, efficacy, and tolerability of rozanolixizumab in CIDP	Phase 2a, multicenter, single arm, OLE study	Rozanolixizumab or placebo sc: Weight-tiered doses of 10mg/kg or 7mg/kg Part 1: Q1W x24 Part 2: Q1W x52	21	59.5 years/ 24 to 79 years
UP0018/ UK	Evaluate safety, PK, and PD of single doses of rozanolixizumab in healthy volunteers	Phase 1, investigator-blind, participant-blind, randomized, placebo-controlled, FIH study evaluating single ascending iv and sc doses of rozanolixizumab	Rozanolixizumab or placebo single dose iv: 1mg/kg, 4mg/kg, 7mg/kg sc: 1mg/kg, 4mg/kg, 7mg/kg	49	44.0 years/ 22 to 65 years
UP0060/UK	Evaluate safety, tolerability, PK, and PD of single ascending doses of rozanolixizumab in Chinese, Japanese, and Caucasian healthy volunteers	Phase 1, single center, randomized, investigator-blind, participant-blind, placebo-controlled, single dose-ascending study	Rozanolixizumab or placebo single dose sc: 4mg/kg, 7mg/kg, 10mg/kg	65	36.5 years/ 20 to 60 years

For the indication of gMG, rozanolixizumab has been evaluated in a completed Phase 3, randomised, double-blind, placebo-controlled study (MG0003), an ongoing Phase 3 randomised OLE study to MG0003 (MG0007), a completed OLE study that was replaced by MG0007 (MG0004), and a completed proof-of-concept Phase 2a study (MG0002).

In MG0003, MG0004, and MG0007 rozanolixizumab was administered at doses ≈7mg/kg or ≈10mg/kg based on a weight-tiered approach with 5 different fixed doses across 4 body weight tiers (Table 6). In MG0002, rozanolixizumab was administered using body weight-based dosing (mg/kg) at doses of 4mg/kg and 7mg/kg.

Safety pools

The safety of rozanolixizumab is compared with placebo following a 6-week double-blind Treatment Period in MG0003. Data from MG0003, MG0004, and MG0007 has also been pooled to investigate the safety profile of rozanolixizumab following repeated Treatment Cycles.

For the purposes of summarising AEs, 2 pools have been defined and for the purposes of immunogenicity analysis, 1 pool has been defined.

Table 67: Overview of safety pools

Pool name/description	Studies included in pool	Analysis Population Size	Purpose of pool
Pool S1/ISAP Amendment 1 Section 3.1.2.1 Study participants who have received ≥1 dose of rozanolixizumab in a 6-week Treatment Period (Figure 7-1)	MG0003 (rozanolixizumab data only) MG0007 MG0004 (first 6 weeks only)	N=196	To calculate exposure To assess the safety of 6-week Treatment Periods
Pool S2/ISAP Amendment 1 Section 3.1.2.2 Study participants who have undergone ≥1 Treatment Cycle with rozanolixizumab (Figure 7-2)	MG0003 (rozanolixizumab data only) MG0007	N=188	To assess the safety of Treatment Cycles (Treatment Period and Follow-up Period)
Pool S3/ISAP Amendment 1 Section 3.1.2.3 Study participants who have **only** received rozanolixizumab under a cyclic treatment regimen (Figure 7-3)	MG0003 (rozanolixizumab data only) MG0007 (excluding data from study participants who were in MG0004)	N=168 (N=98 with ≥2 Treatment Cycles)	To investigate immunogenicity (data provided in the ISI)

N=number of study participants. Note: Treatment Cycle is defined as at least one dose of rozanolixizumab in a 6-week Treatment Period and an (up to) 8-week Follow-up Period starting from the last infusion.

Overall extent of exposure

Placebo-controlled study (MG0003)

Exposure to study treatment (in days) was similar across placebo and rozanolixizumab treatment groups (Table 68). The median duration on study medication was 36.0 days for all treatment groups.

Table 68: MG0003: Study medication duration (SS)

	Placebo N=67	RLZ ≈7mg/kg N=64	RLZ ≈10mg/kg N=69	RLZ Total N=133	All participants N=200
Study medication duration (days)					
Mean (SD)	35.1 (4.1)	35.0 (5.8)	34.8 (6.4)	34.9 (6.1)	35.0 (5.5)
Median (min, max)	36.0 (16, 41)	36.0 (1, 43)	36.0 (1, 43)	36.0 (1, 43)	36.0 (1, 43)

≈=approximate dose; max=maximum; min=minimum; n=number of study participants; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SD=standard deviation; SS=safety set Note: Study medication duration=[(Date of Last Dose Received)-(Date of First Dose Received)]+1

All study participants received at least 1 infusion. The mean number of infusions received was similar across placebo and rozanolixizumab treatment groups (Table 69). A total of 52 (81.3%) study participants in the rozanolixizumab ≈7mg/kg group, 48 (69.6%) in the ≈10mg/kg group, and 56 (83.6%) in the placebo group received all 6 infusions.

Table 69: MG0003: Number of infusions received (SS)

	Placebo N=67	RLZ ≈7mg/kg N=64	RLZ ≈10mg/kg N=69	RLZ Total N=133	All participants N=200
Number of infusions					
Mean (SD)	5.7 (0.6)	5.7 (0.9)	5.5 (1.0)	5.6 (1.0)	5.6 (0.9)
Median (min, max)	6.0 (3, 6)	6.0 (1, 6)	6.0 (1, 6)	6.0 (1, 6)	6.0 (1, 6)
Number of infusions, n (%)					
1	0	1 (1.6)	1 (1.4)	2 (1.5)	2 (1.0)
2	0	1 (1.6)	1 (1.4)	2 (1.5)	2 (1.0)
3	1 (1.5)	0	1 (1.4)	1 (0.8)	2 (1.0)
4	4 (6.0)	3 (4.7)	7 (10.1)	10 (7.5)	14 (7.0)
5	6 (9.0)	7 (10.9)	11 (15.9)	18 (13.5)	24 (12.0)
6	56 (83.6)	52 (81.3)	48 (69.6)	100 (75.2)	156 (78.0)

≈=approximate dose; IMP=investigational medicinal product; n=number of study participants; N=total number of study participants in treatment group; max=maximum; min=minimum; RLZ=rozanolixizumab; SD=standard deviation; SS=safety set
Note: To reduce the potential for unblinding in the event a study participant met protocol-defined criteria for temporary discontinuation of IMP, the participant received a mock infusion

Pool S1

Of the 196 study participants in Pool S1, the total time in Phase 3 gMG studies (including Treatment, Follow-up, and Intermittent Periods) was 188.56 participant-years. At the time of the data cut, 109 of these 196 participants (55.6%) with 140.57 participant-years exposure have undergone at least 1 year of participation in the Phase 3 gMG studies (Table 70), including Treatment, Follow-up, and Intermittent Periods (first 6 weeks of MG0004 only). Study duration of >1/2 year was achieved by 152 (77.6%) participants representing 176.15 participant-years.

Table 70: Time in studies (Pool S1)

Category Statistic	RLZ ≈7mg/kg N=136	RLZ ≈10mg/kg N=145	RLZ Total N=196
Time in study (days) (continuous)			
Sum	33065	35759	68824
Mean (SD)	243.1 (163.7)	246.6 (147.1)	351.1 (161.7)
Median (min, max)	211.5 (24, 639)	246.0 (20, 550)	388.0 (20, 639)
Time in study (categorical), n (%) PY			
>0 years (0 days)	136 (100) 90.59	145 (100) 97.97	196 (100) 188.56
>1/2 year (182 days)	70 (51.5) 73.01	82 (56.6) 80.17	152 (77.6) 176.15
>1 year (365 days)	37 (27.2) 47.15	39 (26.9) 47.19	109 (55.6) 140.57

≈=approximate dose; n=number of study participants with respective time in studies; N=number of study participants who received at least 1 Cycle in the respective treatment group; max=maximum; min=minimum; PY=participant-years; RLZ=rozanolixizumab; SD=standard deviation
Note: Time in study is defined as Treatment Period plus any Observation Period (Follow-up and Intermittent Period).
Note: Participant-years (PY) of therapy are defined as the sum of the time in studies in days for all study participants in the respective dose group divided by 365

Number of cycles

At the time of the data cut, 196 participants in Pool S1 have initiated 748 Cycles of rozanolixizumab. The mean (SD) number of initiated Cycles was 3.8 (2.3) and was balanced across the treatment groups. Until data cut off (08 Jul 2022), 15 (7.6%) participants have started at least 8 Cycles, and 2 (1.0%) participants have started 10 Cycles (Table 71).

Table 71: Number of cycles (Pool S1)

Variable Statistic	RLZ ≈7mg/kg N=136	RLZ ≈10mg/kg N=145	RLZ Total N=196
Number of cycles (continuous)			
Sum	348	400	748
Mean (SD)	2.6 (2.0)	2.8 (2.0)	3.8 (2.3)
Median (min, max)	2.0 (1, 9)	2.0 (1, 8)	3.0 (1, 10)
Number of cycles (categorical), n (%)			
1 cycle	59 (43.4)	55 (37.9)	36 (18.4)
2 cycles	29 (21.3)	33 (22.8)	42 (21.4)
3 cycles	15 (11.0)	14 (9.7)	22 (11.2)
4 cycles	9 (6.6)	14 (9.7)	23 (11.7)
5 cycles	7 (5.1)	8 (5.5)	23 (11.7)
6 cycles	11 (8.1)	9 (6.2)	18 (9.2)
7 cycles	2 (1.5)	9 (6.2)	17 (8.7)
8 cycles	1 (0.7)	3 (2.1)	9 (4.6)
9 cycles	3 (2.2)	0	4 (2.0)
10 cycles	0	0	2 (1.0)

≈=approximate dose; max=maximum; min=minimum; n=number of study participants with respective number of cycles; N=number of study participants who received at least 1 Cycle in the respective treatment group; RLZ=rozanolixizumab; SD=standard deviation
Note: Participants switching RLZ dose between cycles are allocated to both dose groups

2.6.8.2. Adverse events

Overview of adverse events
Placebo-controlled study (MG0003)

Overall, the incidence of TEAEs was similar in the rozanolixizumab ≈7mg/kg and ≈10mg/kg groups (81.3% and 82.6%, respectively) and lower in the placebo group (67.2%; Table 72). No deaths were reported during the study. The incidence of serious TEAEs was similar across placebo and rozanolixizumab ≈7mg/kg and ≈10mg/kg treatment groups (9.0%, 7.8%, and 10.1%, respectively). Severe TEAEs were also more frequent in rozanolixizumab ≈10mg/kg (18.8%) than rozanolixizumab ≈7mg/kg (4.7%) or placebo (4.5%). The incidence of TEAEs considered by the investigator to be related to the IMP was similar in the rozanolixizumab ≈10mg/kg and rozanolixizumab ≈7mg/kg groups (56.5% and 50.0%, respectively) and lower in the placebo group (32.8%).

Table 72: MG0003 Overview of TEAEs (Safety Set)

Category	Placebo N=67 n (%) [#]	RLZ ≈7mg/kg N=64 n (%) [#]	RLZ ≈10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any TEAEs	45 (67.2) [191]	52 (81.3) [208]	57 (82.6) [266]	109 (82.0) [474]
Serious TEAEs	6 (9.0) [6]	5 (7.8) [7]	7 (10.1) [8]	12 (9.0) [15]
Participant discontinuation from study due to TEAEs	2 (3.0) [2]	2 (3.1) [2]	5 (7.2) [6]	7 (5.3) [8]
Permanent discontinuation of IMP due to TEAEs	2 (3.0) [2]	2 (3.1) [2]	4 (5.8) [7]	6 (4.5) [9]
Temporary discontinuation of IMP due to TEAEs	1 (1.5) [1]	3 (4.7) [3]	6 (8.7) [7]	9 (6.8) [10]
Treatment-related TEAEs [a]	22 (32.8) [94]	32 (50.0) [90]	39 (56.5) [139]	71 (53.4) [229]
Severe TEAEs [b]	3 (4.5) [3]	3 (4.7) [4]	13 (18.8) [16]	16 (12.0) [20]
All deaths (AEs leading to death)	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0

≈=approximate dose; [#]=number of individual occurrences of the TEAE in that category; AE=adverse event; CTCAE= Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event. Note: "All deaths" is based on all study participants screened and refers to all deaths occurring on study.
a Based on investigator assessment. b Severe TEAEs are those with CTCAE Grade 3 or above, or those with "severe" intensity as assessed by the investigator

Pool S2

In Pool S2, 169 (89.9%) study participants experienced any TEAE. Across all TEAE categories, the incidence of TEAEs was higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (Table 73).

In general, the incidence of TEAEs across all categories did not increase with repeated cyclic treatment compared with Cycle 1 (Table 73).

Table 73: Overview of TEAEs (Pool S2)

Category	Cycle	Statistic	RLZ ≈7mg/kg N=133 N1=94; N2=69; N3=48; N4=40; N5=28; N6=17; N7=9 Sum of cycles=315	RLZ ≈10mg/kg N=131 N1=94; N2=74; N3=65; N4=52; N5=35; N6=26; N7=15 Sum of cycles=363	RLZ Total N=188 N1=188; N2=143; N3=113; N4=92; N5=63; N6=43; N7=24 Sum of cycles=678
Any TEAE	**All Cycles**	**n (%) [#] {100ER}**	**103 (77.4) [631] {196.8}**	**120 (91.6) [895] {249.6}**	**169 (89.9) [1526] {225.1}**
	Cycle 1	n (%) [#]	68 (72.3) [263]	79 (84.0) [339]	147 (78.2) [602]
	Cycle 2	n (%) [#]	44 (63.8) [153]	56 (75.7) [155]	100 (69.9) [308]
	Cycle 3	n (%) [#]	25 (52.1) [54]	42 (64.6) [131]	67 (59.3) [185]
	Cycle 4	n (%) [#]	19 (47.5) [70]	34 (65.4) [123]	53 (57.6) [193]
	Cycle 5	n (%) [#]	15 (53.6) [45]	31 (88.6) [78]	46 (73.0) [123]
	Cycle 6	n (%) [#]	9 (52.9) [18]	19 (73.1) [55]	28 (65.1) [73]
	Cycle 7	n (%) [#]	5 (55.6) [11]	11 (73.3) [23]	16 (66.7) [34]
Serious TEAEs	**All Cycles**	**n (%) [#] {100ER}**	**14 (10.5) [20] {6.3}**	**29 (22.1) [36] {9.9}**	**42 (22.3) [56] {8.3}**
	Cycle 1	n (%) [#]	7 (7.4) [9]	13 (13.8) [15]	20 (10.6) [24]
	Cycle 2	n (%) [#]	3 (4.3) [5]	6 (8.1) [8]	9 (6.3) [13]
	Cycle 3	n (%) [#]	1 (2.1) [1]	4 (6.2) [5]	5 (4.4) [6]
	Cycle 4	n (%) [#]	2 (5.0) [2]	3 (5.8) [4]	5 (5.4) [6]
	Cycle 5	n (%) [#]	2 (7.1) [3]	4 (11.4) [4]	6 (9.5) [7]
Participant discontinuation due to TEAEs	**All Cycles**	**n (%) [#] {100ER}**	**8 (6.0) [11] {3.5}**	**21 (16.0) [22] {6.1}**	**29 (15.4) [33] {4.9}**
	Cycle 1	n (%) [#]	3 (3.2) [3]	10 (10.6) [11]	13 (6.9) [14]
	Cycle 2	n (%) [#]	3 (4.3) [5]	5 (6.8) [5]	8 (5.6) [10]
	Cycle 3	n (%) [#]	1 (2.1) [2]	2 (3.1) [2]	3 (2.7) [4]
	Cycle 4	n (%) [#]	1 (2.5) [1]	3 (5.8) [3]	4 (4.3) [4]
	Cycle 5	n (%) [#]	0	1 (2.9) [1]	1 (1.6) [1]
Permanent discontinuation of IMP due to TEAEs	**All Cycles**	**n (%) [#] {100ER}**	**8 (6.0) [11] {3.5}**	**19 (14.5) [22] {6.1}**	**27 (14.4) [33] {4.9}**
	Cycle 1	n (%) [#]	3 (3.2) [3]	9 (9.6) [12]	12 (6.4) [15]
	Cycle 2	n (%) [#]	3 (4.3) [5]	5 (6.8) [5]	8 (5.6) [10]
	Cycle 3	n (%) [#]	1 (2.1) [2]	1 (1.5) [1]	2 (1.8) [3]
	Cycle 4	n (%) [#]	1 (2.5) [1]	3 (5.8) [3]	4 (4.3) [4]
	Cycle 5	n (%) [#]	0	1 (2.9) [1]	1 (1.6) [1]
Temporary discontinuation	**All Cycles**	**n (%) [#] {100ER}**	**16 (12.0) [27] {8.6}**	**20 (15.3) [39] {10.7}**	**32 (17.0) [66] {9.7}**
	Cycle 1	n (%) [#]	7 (7.4) [9]	7 (7.4) [8]	14 (7.4) [17]

of IMP due to TEAEs	Cycle 2	n (%) [#]	4 (5.8) [4]	5 (6.8) [6]	9 (6.3) [10]
	Cycle 3	n (%) [#]	2 (4.2) [4]	6 (9.2) [7]	8 (7.1) [11]
	Cycle 4	n (%) [#]	3 (7.5) [3]	5 (9.6) [10]	8 (8.7) [13]
	Cycle 5	n (%) [#]	4 (14.3) [4]	1 (2.9) [2]	5 (7.9) [6]
	Cycle 6	n (%) [#]	1 (5.9) [1]	3 (11.5) [4]	4 (9.3) [5]
	Cycle 7	n (%) [#]	0	1 (6.7) [2]	1 (4.2) [2]
Treatment-related TEAEs	**All Cycles**	**n (%) [#] {100ER}**	**57 (42.9) [248] {77.5}**	**81 (61.8) [424] {117.9}**	**111 (59.0) [672] {99.1}**
	Cycle 1	n (%) [#]	38 (40.4) [113]	56 (59.6) [185]	94 (50.0) [298]
	Cycle 2	n (%) [#]	18 (26.1) [57]	33 (44.6) [83]	51 (35.7) [140]
	Cycle 3	n (%) [#]	8 (16.7) [14]	18 (27.7) [45]	26 (23.0) [59]
	Cycle 4	n (%) [#]	10 (25.0) [32]	18 (34.6) [53]	28 (30.4) [85]
	Cycle 5	n (%) [#]	7 (25.0) [16]	15 (42.9) [28]	22 (34.9) [44]
	Cycle 6	n (%) [#]	6 (35.3) [7]	12 (46.2) [25]	18 (41.9) [32]
	Cycle 7	n (%) [#]	2 (22.2) [2]	6 (40.0) [9]	8 (33.3) [11]
Severe TEAEs	**All Cycles**	**n (%) [#] {100ER}**	**12 (9.0) [21] {6.7}**	**39 (29.8) [55] {15.2}**	**50 (26.6) [76] {11.2}**
	Cycle 1	n (%) [#]	4 (4.3) [5]	19 (20.2) [22]	23 (12.2) [27]
	Cycle 2	n (%) [#]	2 (2.9) [2]	7 (9.5) [8]	9 (6.3) [10]
	Cycle 3	n (%) [#]	1 (2.1) [1]	5 (7.7) [8]	6 (5.3) [9]
	Cycle 4	n (%) [#]	3 (7.5) [9]	5 (9.6) [9]	8 (8.7) [18]
	Cycle 5	n (%) [#]	2 (7.1) [3]	6 (17.1) [7]	8 (12.7) [10]
	Cycle 6	n (%) [#]	1 (5.9) [1]	1 (3.8) [1]	2 (4.7) [2]
TEAEs leading to death	**All Cycles**	**n (%) [#] {100ER}**	**1 (0.8) [1] {0.3}**	**2 (1.5) [2] {0.6}**	**3 (1.6) [3] {0.4}**
	Cycle 2	n (%) [#]	1 (1.4) [1]	1 (1.4) [1]	2 (1.4) [2]
	Cycle 3	n (%) [#]	0	1 (1.5) [1]	1 (0.9) [1]

≈=approximate dose; [#]=number of individual occurrences of the TEAE within the category and cycle; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE within the category and cycle; N=number of study participants with exposure to the respective dose; Ni=number of study participants in each Cycle i=1,2,… in the respective dose group; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event Note: Summaries by Cycle are displayed if the total number of study participants undergoing the Cycle in RLZ Total was ≥10. Note: Summary data and the 100ER in the 'All Cycles' rows are derived from a 'most recent dose' analysis. Data for each individual Cycle are derived from a 'by Cycle' analysis. Therefore, the number of events presented by Cycle may not equal the number of events occurring in All Cycles.

Common TEAE

Placebo-controlled study (MG0003)

A summary of the incidence of TEAEs by PT reported in >2 study participants in a placebo or rozanolixizumab treatment group is provided in Table 74. Treatment-emergent AEs were most frequently reported in the SOCs of nervous system disorders (57.8%, 47.8%, and 31.3% of study participants in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups, respectively) followed by GI disorders (32.8%, 30.4%, and 23.9%, respectively), general disorders and administration site

conditions (25.0%, 39.1%, and 19.4%, respectively), infections and infestations (15.6%, 30.4%, and 19.4%, respectively), and musculoskeletal and connective tissues disorders (23.4%, 18.8%, and 13.4%, respectively).

Table 74: MG0003: Incidence of TEAEs by PT in >2 study participants in a placebo or RLZ treatment group (SS)

MedDRA (v24.0) SOC PT	**Placebo N=67 n (%) [#]**	**RLZ ≈7mg/kg N=64 n (%) [#]**	**RLZ ≈10mg/kg N=69 n (%) [#]**	**RLZ Total N=133 n (%) [#]**
Any TEAE	45 (67.2) [191]	52 (81.3) [208]	57 (82.6) [266]	109 (82.0) [474]
Gastrointestinal disorders	**16 (23.9) [39]**	**21 (32.8) [40]**	**21 (30.4) [39]**	**42 (31.6) [79]**
Diarrhea	9 (13.4) [14]	16 (25.0) [18]	11 (15.9) [18]	27 (20.3) [36]
Nausea	5 (7.5) [12]	5 (7.8) [7]	8 (11.6) [8]	13 (9.8) [15]
Vomiting	1 (1.5) [4]	2 (3.1) [4]	4 (5.8) [4]	6 (4.5) [8]
Abdominal pain upper	2 (3.0) [4]	3 (4.7) [3]	2 (2.9) [2]	5 (3.8) [5]
General disorders and administration site conditions	**13 (19.4) [24]**	**16 (25.0) [24]**	**27 (39.1) [52]**	**43 (32.3) [76]**
Pyrexia	1 (1.5) [1]	8 (12.5) [10]	14 (20.3) [25]	22 (16.5) [35]
Chest pain	0	2 (3.1) [2]	3 (4.3) [4]	5 (3.8) [6]
Infections and infestations	**13 (19.4) [16]**	**10 (15.6) [10]**	**21 (30.4) [24]**	**31 (23.3) [34]**
Nasopharyngitis	3 (4.5) [4]	1 (1.6) [1]	5 (7.2) [5]	6 (4.5) [6]
Urinary tract infection	4 (6.0) [4]	2 (3.1) [2]	2 (2.9) [2]	4 (3.0) [4]
Oral herpes	0	0	3 (4.3) [3]	3 (2.3) [3]
Injury, poisoning and procedural complications	**5 (7.5) [10]**	**5 (7.8) [5]**	**4 (5.8) [6]**	**9 (6.8) [11]**
Fall	3 (4.5) [3]	0	2 (2.9) [4]	2 (1.5) [4]
Musculoskeletal and connective tissue disorders	**9 (13.4) [13]**	**15 (23.4) [30]**	**13 (18.8) [19]**	**28 (21.1) [49]**
Arthralgia	2 (3.0) [2]	4 (6.3) [6]	5 (7.2) [5]	9 (6.8) [11]
Myalgia	1 (1.5) [1]	2 (3.1) [9]	4 (5.8) [4]	6 (4.5) [13]
Muscle spasms	1 (1.5) [1]	3 (4.7) [4]	0	3 (2.3) [4]
Nervous system disorders	**21 (31.3) [52]**	**37 (57.8) [70]**	**33 (47.8) [65]**	**70 (52.6) 135**

Headache	13 (19.4) [31]	29 (45.3) [54]	26 (37.7) [52]	55 (41.4) [106]
Myasthenia gravis	3 (4.5) [3]	3 (4.7) [3]	3 (4.3) [3]	6 (4.5) [6]
Somnolence	3 (4.5) [8]	1 (1.6) [1]	0	1 (0.8) [1]
Renal and urinary disorders	**2 (3.0) [2]**	**1 (1.6) [2]**	**4 (5.8) [6]**	**5 (3.8) [8]**
Renal impairment	0	0	3 (4.3) [3]	3 (2.3) [3]
Respiratory, thoracic and mediastinal disorders	**4 (6.0) [6]**	**4 (6.3) [6]**	**7 (10.1) [7]**	**11 (8.3) [13]**
Oropharyngeal pain	1 (1.5) [1]	0	3 (4.3) [3]	3 (2.3) [3]
Skin and subcutaneous tissue disorders	**4 (6.0) [4]**	**6 (9.4) [6]**	**11 (15.9) [12]**	**17 (12.8) [18]**
Rash	0	3 (4.7) [3]	3 (4.3) [3]	6 (4.5) [6]
Vascular disorders	**1 (1.5) [1]**	**7 (10.9) [7]**	**6 (8.7) [8]**	**13 (9.8) [15]**
Hypertension	0	5 (7.8) [5]	0	5 (3.8) [5]

≈=approximate dose; [#]=number of individual occurrences of the TEAE; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAE within SOC/PT; N=total number of study participants in treatment group; PT=preferred term; RLZ=rozanolixizumab; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event

Pool S2

In total, 169 (89.9%) study participants experienced 1526 TEAEs in Pool S2. The incidence of TEAEs was higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (91.6% vs 77.4% of participants) (Table 75).

Table 75: Incidence of TEAEs by PT in ≥5% of study participants in any treatment group, and Cycle-adjusted TEAE rates by most recent dose (Pool S2)

MedDRA (v24.0) **SOC** **PT**	**Statistic**	**RLZ ≈7mg/kg N=133** **Sum of all cycles=315**	**RLZ ≈10mg/kg N=131** **Sum of all cycles=363**	**RLZ Total N=188** **Sum of all cycles=678**
Any TEAE	n (%) [#] {100ER}	103 (77.4) [631] {196.8}	120 (91.6) [895] {249.6}	169 (89.9) [1526] {225.1}
Gastrointestinal disorders	**n (%) [#] {100ER}**	**41 (30.8) [105] {33.3}**	**54 (41.2) [142] {39.1}**	**80 (42.6) [247] {36.4}**
Diarrhoea	n (%) [#] {100ER}	30 (22.6) [47] {14.9}	30 (22.9) [52] {14.3}	54 (28.7) [99] {14.6}
Abdominal pain	n (%) [#] {100ER}	8 (6.0) [8] {2.5}	7 (5.3) [10] {2.8}	15 (8.0) [18] {2.7}
Abdominal pain upper	n (%) [#] {100ER}	4 (3.0) [4] {1.3}	7 (5.3) [9] {2.5}	10 (5.3) [13] {1.9}
Nausea	n (%) [#] {100ER}	13 (9.8) [21] {6.7}	19 (14.5) [26] {7.2}	28 (14.9) [47] {6.9}
Vomiting	n (%) [#] {100ER}	4 (3.0) [7] {2.2}	10 (7.6) [10] {2.8}	13 (6.9) [17] {2.5}
General disorders and administration site conditions	**n (%) [#] {100ER}**	**39 (29.3) [82] {26.0}**	**56 (42.7) [114] {31.4}**	**80 (42.6) [196] {28.9}**
Asthenia	n (%) [#] {100ER}	4 (3.0) [5] {1.6}	6 (4.6) [7] {1.9}	10 (5.3) [12] {1.8}
Pyrexia	n (%) [#] {100ER}	14 (10.5) [24] {7.6}	24 (18.3) [41] {11.3}	34 (18.1) [65] {9.6}
Influenza like illness	n (%) [#] {100ER}	3 (2.3) [3] {1.0}	7 (5.3) [7] {1.9}	9 (4.8) [10] {1.5}
Oedema peripheral	n (%) [#] {100ER}	2 (1.5) [3] {1.0}	7 (5.3) [8] {2.2}	9 (4.8) [11] {1.6}
Chest pain	n (%) [#] {100ER}	3 (2.3) [3] {1.0}	7 (5.3) [8] {2.2}	9 (4.8) [11] {1.6}
Infections and infestations	**n (%) [#] {100ER}**	**43 (32.3) [73] {22.5}**	**54 (41.2) [94] {26.4}**	**85 (45.2) [167] {24.6}**
COVID-19	n (%) [#] {100ER}	11 (8.3) [12] {3.8}	15 (11.5) [16] {4.4}	26 (13.8) [28] {4.1}
Oral herpes	n (%) [#] {100ER}	1 (0.8) [1] {0.3}	8 (6.1) [10] {2.8}	9 (4.8) [11] {1.6}
Nasopharyngitis	n (%) [#] {100ER}	6 (4.5) [11] {3.2}	8 (6.1) [8] {2.5}	13 (6.9) [19] {2.8}
Upper respiratory tract infection	n (%) [#] {100ER}	5 (3.8) [7] {2.2}	8 (6.1) [11] {3.0}	13 (6.9) [18] {2.7}

Injury, poisoning and procedural complications	**n (%) [#] {100ER}**	**13 (9.8) [17] {5.4}**	**18 (13.7) [26] {7.2}**	**28 (14.9) [43] {6.3}**
Fall	n (%) [#] {100ER}	3 (2.3) [3] {1.0}	7 (5.3) [10] {2.8}	9 (4.8) [13] {1.9}
Investigations	**n (%) [#] {100ER}**	**14 (10.5) [23] {7.3}**	**35 (26.7) [67] {18.5}**	**47 (25.0) [90] {13.3}**
Blood immunoglobulin G decreased	n (%) [#] {100ER}	6 (4.5) [12] {3.8}	14 (10.7) [21] {5.8}	20 (10.6) [33] {4.9}
Musculoskeletal and connective tissue disorders	**n (%) [#] {100ER}**	**33 (24.8) [57] {17.8}**	**33 (25.2) [56] {15.7}**	**59 (31.4) [113] {16.7}**
Arthralgia	n (%) [#] {100ER}	9 (6.8) [12] {3.8}	12 (9.2) [14] {3.9}	21 (11.2) [26] {3.8}
Myalgia	n (%) [#] {100ER}	2 (1.5) [9] {2.9}	8 (6.1) [8] {2.2}	10 (5.3) [17] {2.5}
Nervous system disorders	**n (%) [#] {100ER}**	**65 (48.9) [152] {46.3}**	**73 (55.7) [231] {65.3}**	**112 (59.6) [383] {56.5}**
Headache	n (%) [#] {100ER}	54 (40.6) [116] {35.9}	55 (42.0) [181] {50.7}	87 (46.3) [297] {43.8}
Dizziness	n (%) [#] {100ER}	1 (0.8) [1] {0.3}	9 (6.9) [9] {2.5}	10 (5.3) [10] {1.5}
Myasthenia gravis	n (%) [#] {100ER}	7 (5.3) [9] {2.9}	11 (8.4) [13] {3.6}	18 (9.6) [22] {3.2}
Skin and subcutaneous tissue disorders	**n (%) [#] {100ER}**	**19 (14.3) [31] {9.8}**	**20 (15.3) [29] {8.0}**	**35 (18.6) [60] {8.8}**
Rash	n (%) [#] {100ER}	5 (3.8) [9] {2.9}	6 (4.6) [8] {2.2}	11 (5.9) [17] {2.5}
Vascular disorders	**n (%) [#] {100ER}**	**8 (6.0) [8] {2.5}**	**19 (14.5) [25] {6.9}**	**26 (13.8) [33] {4.9}**
Hypertension	n (%) [#] {100ER}	5 (3.8) [5] {1.6}	7 (5.3) [9] {2.5}	12 (6.4) [14] {2.1}

≈=approximate dose; [#]=number of individual occurrences of the TEAE within the SOC/PT category for most recent dose; 100ER=number of TEAEs occurring in the respective dose divided by the sum of cycles from all study participants in the respective dose and multiplied by 100; COVID 19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAE within the SOC/PT category; N=number of study participants treated with exposure to the respective dose; PT=preferred term; RLZ=rozanolixizumab; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Summary data and the 100ER are derived from a 'most recent dose' analysis.

Overall, the incidence of any TEAEs did not increase with repeated treatment cycles, including in the most common SOCs of Nervous System Disorders, Infections and infestations, and Gastrointestinal Disorders. With repeated cyclic treatment, the incidence of the most common TEAEs of headache, diarrhoea, pyrexia, nausea, and arthralgia, did not increase, while a trend for an increase in the incidence of blood IgG decrease was observed (Table 76).

Table 76: Incidence of TEAEs by PT and Treatment Cycle in ≥5% of study participants in the RLZ total group in any Treatment Cycle (Pool S2)

MedDRA (v24.0) PT	Cycle 1 RLZ Total N=188 n (%) [#]	Cycle 2 RLZ Total N=143 n (%) [#]	Cycle 3 RLZ Total N=113 n (%) [#]	Cycle 4 RLZ Total N=92 n (%) [#]	Cycle 5 RLZ Total N=63 n (%) [#]	Cycle 6 RLZ Total N=43 n (%) [#]	Cycle 7 RLZ Total N=24 n (%) [#]
Any TEAE	147 (78.2) [602]	100 (69.9) [308]	67 (59.3) [185]	53 (57.6) [193]	46 (73.0) [123]	28 (65.1) [73]	16 (66.7) [34]
Headache	69 (36.7) [131]	34 (23.8) [59]	21 (18.6) [36]	16 (17.4) [38]	10 (15.9) [12]	9 (20.9) [13]	5 (20.8) [7]
Diarrhoea	36 (19.1) [48]	11 (7.7) [15]	7 (6.2) [9]	9 (9.8) [14]	7 (11.1) [9]	3 (7.0) [3]	1 (4.2) [1]
Pyrexia	25 (13.3) [38]	9 (6.3) [10]	2 (1.8) [2]	5 (5.4) [7]	2 (3.2) [4]	3 (7.0) [4]	0
Nausea	15 (8.0) [18]	9 (6.3) [10]	6 (5.3) [7]	4 (4.3) [7]	4 (6.3) [4]	0	0
Arthralgia	10 (5.3) [12]	4 (2.8) [4]	2 (1.8) [2]	6 (6.5) [6]	0	2 (4.7) [2]	0
Myasthenia gravis	9 (4.8) [9]	2 (1.4) [4]	2 (1.8) [2]	2 (2.2) [2]	4 (6.3) [5]	0	0
Vomiting	6 (3.2) [8]	2 (1.4) [2]	2 (1.8) [2]	1 (1.1) [1]	1 (1.6) [1]	1 (2.3) [1]	2 (8.3) [2]
COVID-19	4 (2.1) [5]	10 (7.0) [10]	5 (4.4) [5]	4 (4.3) [5]	1 (1.6) [1]	2 (4.7) [2]	0
Blood immunoglobulin G decreased	4 (2.1) [4]	7 (4.9) [7]	5 (4.4) [7]	7 (7.6) [7]	5 (7.9) [5]	3 (7.0) [3]	0
Upper respiratory tract infection	3 (1.6) [3]	4 (2.8) [5]	1 (0.9) [1]	1 (1.1) [1]	4 (6.3) [5]	2 (4.7) [2]	1 (4.2) [1]

[#]=number of individual occurrences of the TEAE within the PT category and cycle; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAE within the PT category and cycle; N=number of study participants treated with RLZ at least once; PT=preferred term; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event Note: Summaries by Cycle are displayed if the total number of study participants undergoing the Cycle in RLZ Total was ≥10. Note: Data for each individual Cycle are derived from a 'by Cycle' analysis.

Severe TEAEs

Placebo-controlled study (MG0003)

In MG0003, TEAEs were predominantly mild or moderate in intensity in all treatment groups. The incidence of severe TEAEs was higher in the rozanolixizumab ≈10mg/kg group (13 [18.8%] participants) than in the rozanolixizumab ≈7mg/kg (3 [4.7%] participants) and placebo (3 [4.5%] participants) groups (Table 81). Severe TEAEs most frequently occurred in the SOC Nervous System Disorders. Within this SOC, headache was the most common severe TEAE and drove the imbalance between the ≈10mg/kg and ≈7mg/kg treatment groups (6 [8.7%] and 1 [1.6%] participants, respectively). No placebo-treated participant experienced severe headache. The other TEAEs of severe intensity occurring in >1 study participant in the rozanolixizumab ≈10mg/kg or ≈7mg/kg treatment groups were diarrhoea (0 and 2 [2.9%] participants, respectively, vs 0 in placebo) and myasthenia gravis (1 [1.6%] and 2 [2.9%], respectively vs 1 [1.5%] in placebo. All other TEAEs of severe intensity occurred in no more than 1 study participant.

Table 77: Severe TEAEs Study MG003 (Safety Set)

MedDRA 24.0 System Organ Class High Level Term Preferred Term	Placebo N=67 n (%) [#]	RLZ ~7mg/kg N=64 n (%) [#]	RLZ ~10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any severe TEAE [a]	3 (4.5) [3]	3 (4.7) [4]	13 (18.8) [16]	16 (12.0) [20]
Blood and lymphatic system disorders	0	0	1 (1.4) [1]	1 (0.8) [1]
Leukopenias NEC	0	0	1 (1.4) [1]	1 (0.8) [1]
Lymphopenia	0	0	1 (1.4) [1]	1 (0.8) [1]
Gastrointestinal disorders	0	1 (1.6) [1]	2 (2.9) [2]	3 (2.3) [3]
Diarrhoea (excl infective)	0	0	2 (2.9) [2]	2 (1.5) [2]
Diarrhoea	0	0	2 (2.9) [2]	2 (1.5) [2]
Nausea and vomiting symptoms	0	1 (1.6) [1]	0	1 (0.8) [1]
Vomiting	0	1 (1.6) [1]	0	1 (0.8) [1]
Musculoskeletal and connective tissue disorders	1 (1.5) [1]	1 (1.6) [1]	0	1 (0.8) [1]
Joint related signs and symptoms	0	1 (1.6) [1]	0	1 (0.8) [1]
Arthralgia	0	1 (1.6) [1]	0	1 (0.8) [1]
Muscle weakness conditions	1 (1.5) [1]	0	0	0
Muscular weakness	1 (1.5) [1]	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (1.4) [1]	1 (0.8) [1]
Neoplasms malignant site unspecified NEC	0	0	1 (1.4) [1]	1 (0.8) [1]
Metastatic squamous cell carcinoma	0	0	1 (1.4) [1]	1 (0.8) [1]
Nervous system disorders	2 (3.0) [2]	2 (3.1) [2]	8 (11.6) [8]	10 (7.5) [10]
Headaches NEC	0	1 (1.6) [1]	6 (8.7) [6]	7 (5.3) [7]
Headache	0	1 (1.6) [1]	6 (8.7) [6]	7 (5.3) [7]
Neuromuscular junction dysfunction	2 (3.0) [2]	1 (1.6) [1]	2 (2.9) [2]	3 (2.3) [3]
Myasthenia gravis	1 (1.5) [1]	1 (1.6) [1]	2 (2.9) [2]	3 (2.3) [3]
Myasthenia gravis crisis	1 (1.5) [1]	0	0	0
Product issues	0	0	1 (1.4) [1]	1 (0.8) [1]
Device issues NEC	0	0	1 (1.4) [1]	1 (0.8) [1]
Device dislocation	0	0	1 (1.4) [1]	1 (0.8) [1]
Renal and urinary disorders	0	0	1 (1.4) [1]	1 (0.8) [1]
Renal lithiasis	0	0	1 (1.4) [1]	1 (0.8) [1]
Nephrolithiasis	0	0	1 (1.4) [1]	1 (0.8) [1]
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.4) [1]	1 (0.8) [1]
Respiratory failures (excl neonatal)	0	0	1 (1.4) [1]	1 (0.8) [1]
Acute respiratory failure	0	0	1 (1.4) [1]	1 (0.8) [1]
Vascular disorders	0	0	1 (1.4) [1]	1 (0.8) [1]
Peripheral embolism and thrombosis	0	0	1 (1.4) [1]	1 (0.8) [1]
Deep vein thrombosis	0	0	1 (1.4) [1]	1 (0.8) [1]

~=equivalent dose, IMP=Investigational Medicinal Product, MedDRA=Medical Dictionary for Regulatory Activities, RLZ=Rozanolixizumab, TEAE=Treatment-Emergent Adverse Event
[a] Severe TEAEs are those with CTCAE Grade 3 or above, or those with intensity as 'severe' by the Investigator. Note: n=number of participants reporting at least one TEAE within System Organ Class/High Level Term/Preferred Term.
Note: [#] is the number of individual occurrences of the TEAE.

Pool S2

In total, 50 (26.6%) study participants experienced TEAEs of severe intensity in Pool S2 (Table 78), with incidence higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (39 [29.8%] vs 12 [9.0%]).

Table 78: Incidence of severe TEAEs by PT and Treatment Cycle in ≥2 study participants in the RLZ total group and Cycle-adjusted TEAE rates (Pool S2)

MedDRA (v24.0) PT	All Cycles Sum of cycles=678 RLZ Total N=188 n (%) [#] {100ER}	Cycle 1 RLZ Total N=188 n (%) [#]	Cycle 2 RLZ Total N=143 n (%) [#]	Cycle 3 RLZ Total N=113 n (%) [#]	Cycle 4 RLZ Total N=92 n (%) [#]	Cycle 5 RLZ Total N=63 n (%) [#]	Cycle 6 RLZ Total N=43 n (%) [#]	Cycle 7 RLZ Total N=24 n (%) [#]
Any severe TEAE	**50 (26.6) [76] {11.2}**	23 (12.2) [27]	9 (6.3) [10]	6 (5.3) [9]	8 (8.7) [18]	8 (12.7) [10]	2 (4.7) [2]	0
Headache	**8 (4.3) [8] {1.2}**	7 (3.7) [7]	0	0	0	0	1 (2.3) [1]	0
Myasthenia gravis	**11 (5.9) [13] {1.9}**	5 (2.7) [5]	1 (0.7) [1]	2 (1.8) [2]	1 (1.1) [1]	3 (4.8) [4]	0	0
Diarrhoea	**2 (1.1) [2] {0.3}**	2 (1.1) [2]	0	0	0	0	0	0
Myasthenia gravis crisis	**4 (2.1) [4] {0.6}**	1 (0.5) [1]	2 (1.4) [2]	1 (0.9) [1]	0	0	0	0
Lymphopenia	**2 (1.1) [3] {0.4}**	1 (0.5) [1]	1 (0.7) [2]	0	0	0	0	0
Nephrolithiasis	**2 (1.1) [2] {0.3}**	1 (0.5) [1]	0	0	0	0	1 (2.3) [1]	0
COVID-19	**2 (1.1) [2] {0.3}**	0	1 (0.7) [1]	0	1 (1.1) [1]	0	0	0
Blood immunoglobulin G decreased	**4 (2.1) [5] {0.7}**	0	0	1 (0.9) [1]	3 (3.3) [3]	1 (1.6) [1]	0	0

[#]=number of individual occurrences of the severe TEAE within the PT category and cycle; 100ER=number of severe TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 severe TEAE within the PT category and cycle; N=number of study participants treated with RLZ at least once; PT=preferred term; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event Note: Summaries by Cycle are displayed if the total number of study participants experiencing the event undergoing the Cycle in RLZ Total was ≥10. Note: Summary data and the 100ER in the 'Sum of Cycles' column are derived from a 'most recent dose' analysis. Data for each individual Cycle are derived from a 'by Cycle' analysis. Therefore, the number of events presented by Cycle may not equal the number of events occurring in All Cycles

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

In total, 5 participants died including 4 participants who died before the data cutoff (08 Jul 2022), and 1 participant who died post data cutoff. Of the 4 participants who died before the data cut off, 2 participants had TEAEs leading to death, 1 participant had TEAEs and non-TEAEs leading to death, and 1 participant had a non-TEAE leading to death. All deaths occurred in MG0007.

Serious adverse events

Placebo-controlled study (MG0003)

The incidence of serious TEAEs was low and similar across the rozanolixizumab ≈7mg/kg (7.8% of participants), rozanolixizumab ≈10mg/kg (10.1%), and placebo (9.0%) groups (Table 79).

The most frequent serious TEAEs were related to MG worsening and comprised myasthenia gravis (1.6%, 2.9%, and 1.5% participants) and myasthenia gravis crisis (0, 0, and 3.0%) in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo group, respectively.

Table 79: MG0003: Incidence of serious TEAEs (SS)

MedDRA (v24.0) SOC PT	Placebo N=67 n (%) [#]	RLZ ≈7mg/kg N=64 n (%) [#]	RLZ ≈10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any serious TEAE	6 (9.0) [6]	5 (7.8) [7]	7 (10.1) [8]	12 (9.0) [15]
Gastrointestinal disorders	**0**	**2 (3.1) [2]**	**0**	**2 (1.5) [2]**
Gastritis	0	1 (1.6) [1]	0	1 (0.8) [1]
Vomiting	0	1 (1.6) [1]	0	1 (0.8) [1]
General disorders and administration site conditions	**0**	**0**	**1 (1.4) [1]**	**1 (0.8) [1]**
Chest pain	0	0	1 (1.4) [1]	1 (0.8) [1]
Infections and infestations	**1 (1.5) [1]**	**0**	**0**	**0**
COVID-19 pneumonia	1 (1.5) [1]	0	0	0
Injury, poisoning and procedural complications	**1 (1.5) [1]**	**0**	**0**	**0**
Thoracic vertebral fracture	1 (1.5) [1]	0	0	0
Musculoskeletal and connective tissue disorders	**1 (1.5) [1]**	**1 (1.6) [2]**	**0**	**1 (0.8) [2]**
Arthralgia	0	1 (1.6) [2]	0	1 (0.8) [2]
Muscular weakness	1 (1.5) [1]	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (1.4) [1]**	**1 (0.8) [1]**
Metastatic squamous cell carcinoma	0	0	1 (1.4) [1]	1 (0.8) [1]
Nervous system disorders	**3 (4.5) [3]**	**2 (3.1) [2]**	**3 (4.3) [3]**	**5 (3.8) [5]**
Headache	0	0	1 (1.4) [1]	1 (0.8) [1]
Myasthenia gravis	1 (1.5) [1]	1 (1.6) [1]	2 (2.9) [2]	3 (2.3) [3]
Myasthenia gravis crisis	2 (3.0) [2]	0	0	0
Seizure	0	1 (1.6) [1]	0	1 (0.8) [1]
Product issues	**0**	**0**	**1 (1.4) [1]**	**1 (0.8) [1]**
Device dislocation	0	0	1 (1.4) [1]	1 (0.8) [1]
Renal and urinary disorders	**0**	**0**	**1 (1.4) [1]**	**1 (0.8) [1]**
Nephrolithiasis	0	0	1 (1.4) [1]	1 (0.8) [1]
Reproductive system and breast disorders	**0**	**1 (1.6) [1]**	**0**	**1 (0.8) [1]**
Cervical dysplasia	0	1 (1.6) [1]	0	1 (0.8) [1]
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (1.4) [1]**	**1 (0.8) [1]**
Acute respiratory failure	0	0	1 (1.4) [1]	1 (0.8) [1]

≈=approximate dose; [#]=number of individual occurrences of the TEAE; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 serious TEAE within SOC/PT; N=total number of study participants in treatment group; PT=preferred term; RLZ=rozanolixizumab; SOC=system organ class; SS=Safety Set; TEAE=Treatment-Emergent Adverse Event

Pool S2

In Pool S2, 42 (22.3%) study participants experienced 56 serious TEAEs (Table 80). Overall, serious TEAEs were most frequently reported in the SOCs of Nervous system disorders (19 [10.1%] participants), Infections and infestations (8 [4.3%]), and Gastrointestinal disorders (5 [2.7%]). The only serious TEAEs occurring in >1 participant were myasthenia gravis (12 [6.4%] participants), myasthenia gravis crisis (4 [2.1%], and COVID-19 (3 [1.6%]). Although the incidence of serious TEAEs was higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (29 [22.1%] vs 14 [10.5%] participants), this difference was predominantly driven by serious TEAEs of myasthenia gravis (8 [6.1%] vs 4 [3.0%]), myasthenia gravis crisis (4 [3.1%] vs 0), and serious TEAEs with a single incidence occurring more frequently at the higher dose.

There was 1 case of subacute cutaneous lupus erythematosus (SCLE). This participant previously treated with rozanolixizumab ≈7mg/kg, with medical history of other autoimmune conditions, experienced a serious and severe TEAE of SCLE, 30 days after the last dose of rozanolixizumab ≈7mg/kg.

Compared with Cycle 1, the incidence of serious TEAEs did not increase with repeated cyclic treatment. At the time of the data cut-off, there were no serious TEAEs in Cycles 6 and 7. (Table 80).

Table 80: Incidence of serious TEAEs by PT and Treatment Cycle in ≥2 study participants in the RLZ total group and Cycle-adjusted TEAE rates (Pool S2)

MedDRA (v24.0) PT	All Cycles Sum of cycles=678 RLZ Total N=188 n (%) [#] {100ER}	Cycle 1 RLZ Total N=188 n (%) [#]	Cycle 2 RLZ Total N=143 n (%) [#]	Cycle 3 RLZ Total N=113 n (%) [#]	Cycle 4 RLZ Total N=92 n (%) [#]	Cycle 5 RLZ Total N=63 n (%) [#]	Cycle 6 RLZ Total N=43 n (%) [#]	Cycle 7 RLZ Total N=24 n (%) [#]
Any serious TEAE	**42 (22.3) [56] {8.3}**	20 (10.6) [24]	9 (6.3) [13]	5 (4.4) [6]	5 (5.4) [6]	6 (9.5) [7]	0	0
Myasthenia gravis	**12 (6.4) [16] {2.4}**	5 (2.7) [5]	2 (1.4) [4]	2 (1.8) [2]	1 (1.1) [1]	3 (4.8) [4]	0	0
Myasthenia gravis crisis	**4 (2.1) [4] {0.6}**	1 (0.5) [1]	2 (1.4) [2]	1 (0.9) [1]	0	0	0	0
COVID-19	**3 (1.6) [3] {0.4}**	1 (0.5) [1]	1 (0.7) [1]	0	1 (1.1) [1]	0	0	0

[#]=number of individual occurrences of the serious TEAE within PT category and cycle; 100ER=number of serious TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; COVID19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 serious TEAE within the PT category and cycle; N=number of study participants treated with RLZ at least once; PT=preferred term; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event Note: Summary data and the 100ER in the in the 'Sum of Cycles' column are derived from a 'most recent dose' analysis. Data for each individual Cycle are derived from a 'by Cycle' analysis. Therefore, the number of events presented by Cycle may not equal the number of events occurring in All Cycles.

Adverse events of focus

Headache

Placebo-controlled study (MG0003)

In total, TEAEs meeting criteria for headache occurred in 31 (48.4%), 27 (39.1%), and 13 (19.4%) participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. Most study participants had events that were of mild or moderate maximum intensity (Table 81). Severe events occurred in 1 (1.6%) and 6 (8.7%) study participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg group, respectively, and led to study discontinuation for the participant in the rozanolixizumab ≈7mg/kg group.

Table 81: MG0003: Incidence of TEAEs by PT with HLGT headache by maximum intensity (SS)

Preferred term Intensity	Placebo N=67 n (%)	RLZ ≈7mg/kg N=64 n (%)	RLZ ≈10mg/kg N=69 n (%)
Headache (all intensities)	**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 (all intensities)	**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

≈=approximate dose; HLGT=high-level group term; n=number of study participants with at least 1 TEAE within the HLGT; n=number of study participants reporting at least 1 TEAE in that category; N=total number of study participants in treatment group; PT=preferred term; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event Note: Each study participant was counted once within the preferred term according to the maximum intensity for all TEAEs

Pool S2

In total, 89 (47.3%) study participants experienced any headache in Pool S2 (Table 82), with the incidence similar across the ≈7mg/kg and ≈10mg/kg dose groups, and higher during the Treatment Period compared with the Follow-up Period. Compared with Cycle 1, the incidence of any headache did not increase with repeated cyclic treatment (Table 82).

Table 82: Incidence of headache by PT and treatment cycle in the RLZ total group and cycle-adjusted TEAE rates (Pool S2)

MedDRA (v24.0) PT	All Cycles Sum of cycles=678 RLZ Total N=188 n (%) [#] {100ER}	Cycle 1 RLZ Total N=188 n (%) [#]	Cycle 2 RLZ Total N=143 n (%) [#]	Cycle 3 RLZ Total N=113 n (%) [#]	Cycle 4 RLZ Total N=92 n (%) [#]	Cycle 5 RLZ Total N=63 n (%) [#]	Cycle 6 RLZ Total N=43 n (%) [#]	Cycle 7 RLZ Total N=24 n (%) [#]
Any headache	**89 (47.3) [306]** **{45.1}**	72 (38.3) [137]	34 (23.8) [59]	21 (18.6) [37]	17 (18.5) [40]	10 (15.9) [12]	9 (20.9) [13]	5 (20.8) [7]
Headache	**87 (46.3) [297]** **{43.8}**	69 (36.7) [131]	34 (23.8) [59]	21 (18.6) [36]	16 (17.4) [38]	10 (15.9) [12]	9 (20.9) [13]	5 (20.8) [7]
Migraine	**5 (2.7) [8]** **{1.2}**	4 (2.1) [6]	0	0	1 (1.1) [2]	0	0	0
Migraine with aura	**1 (0.5) [1]** **{0.1}**	0	0	1 (0.9) [1]	0	0	0	0

[#]=number of individual occurrences of the TEAEOF within the PT category and cycle; 100ER=number of TEAEOF occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAEOF within the PT category and cycle; N=number of study participants treated with the dose at least once; PT=preferred term; RLZ=rozanolixizumab; TEAE=treatment-emergent adverse event; TEAEOF=treatment emergent adverse event of focus Note: Summaries by Cycle are displayed if the total number of study participants experiencing the event undergoing the Cycle in RLZ Total was ≥10. Note: Summary data and the 100ER in the in the 'Sum of Cycles' column are derived from a 'most recent dose' analysis. Data for each individual Cycle are derived from a 'by Cycle' analysis. Therefore, the number of events presented by Cycle may not equal the number of events occurring in All Cycles.

Infections, including opportunistic infections

Placebo-controlled study (MG0003)

In total, 31 (23.3%) rozanolixizumab-treated participants and 13 (19.4%) placebo-treated participants reported TEAEs within the infections and infestations SOC. Overall, the incidence of infections was similar between the rozanolixizumab and placebo treatment groups; however, incidence was higher with rozanolixizumab ≈10mg/kg group (21 [30.4%] participants) compared with placebo (13 [19.4%]).

Pool S2

Any infections:

In total, 85 (45.2%) study participants experienced a TEAE within the SOC Infections and infestations in Pool S2, including 43 (32.3%) and 54 (41.2%) participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively (Table 83). The most common infections by PT were COVID-19, upper respiratory tract infection, nasopharyngitis, and oral herpes (Table 83). The incidence of TEAEs within this SOC did not increase with repeated cyclic treatment. In total, TEAEs within this SOC led to discontinuations from the study and/or IMP in <5% of participants (both 6 [3.2%] participants).

Table 83: Incidence of TEAEs occurring in the SOC Infections and Infestations by PT and Treatment Cycle in ≥2 study participants in the RLZ total group and cycle-adjusted TEAE rates (Pool S2)

MedDRA (v24.0) PT	All Cycles Sum of cycles=572 RLZ Total N=188 n (%) [#] {100ER}	Cycle 1 RLZ Total N=188 n (%) [#]	Cycle 2 RLZ Total N=143 n (%) [#]	Cycle 3 RLZ Total N=113 n (%) [#]	Cycle 4 RLZ Total N=92 n (%) [#]	Cycle 5 RLZ Total N=63 n (%) [#]	Cycle 6 RLZ Total N=43 n (%) [#]	Cycle 7 RLZ Total N=24 n (%) [#]
Any infection or infestations	**85 (45.2) [167] {24.6}**	43 (22.9) [48]	24 (16.8) [30]	25 (22.1) [27]	16 (17.4) [25]	19 (30.2) [21]	8 (18.6) [11]	3 (12.5) [3]
Nasopharyngitis	**13 (6.9) [19] {2.8}**	7 (3.7) [7]	0	5 (4.4) [5]	3 (3.3) [4]	2 (3.2) [2]	0	0
COVID-19	**26 (13.8) [28] {4.1}**	4 (2.1) [5]	10 (7.0) [10]	5 (4.4) [5]	4 (4.3) [5]	1 (1.6) [1]	2 (4.7) [2]	0
Oral herpes	**9 (4.8) [11] {1.6}**	4 (2.1) [4]	3 (2.1) [3]	1 (0.9) [1]	0	2 (3.2) [2]	1 (2.3) [1]	0
Urinary tract infection	**7 (3.7) [11] {1.6}**	4 (2.1) [4]	1 (0.7) [1]	1 (0.9) [1]	1 (1.1) [1]	2 (3.2) [2]	1 (2.3) [1]	0
Upper respiratory tract infection	**13 (6.9) [18] {2.7}**	3 (1.6) [3]	4 (2.8) [5]	1 (0.9) [1]	1 (1.1) [1]	4 (6.3) [5]	2 (4.7) [2]	1 (4.2) [1]
Herpes zoster	**4 (2.1) [4] {0.6}**	3 (1.6) [3]	1 (0.7) [1]	0	0	0	0	0
Conjunctivitis	**3 (1.6) [3] {0.4}**	2 (1.1) [2]	1 (0.7) [1]	0	0	0	0	0
Respiratory tract infection viral	**3 (1.6) [5] {0.7}**	2 (1.1) [2]	1 (0.7) [1]	1 (0.9) [1]	0	1 (1.6) [1]	0	0
Sinusitis	**3 (1.6) [5] {0.7}**	1 (0.5) [1]	0	1 (0.9) [1]	0	1 (1.6) [1]	1 (2.3) [1]	1 (4.2) [1]

Cellulitis	**2 (1.1) [2] {0.3}**	2 (1.1) [2]	0	0	0	0	0	0
Tooth abscess	**2 (1.1) [2] {0.3}**	2 (1.1) [2]	0	0	0	0	0	0
Cystitis	**2 (1.1) [2] {0.3}**	2 (1.1) [2]	0	0	0	0	0	0
Pneumonia	**2 (1.1) [2] {0.3}**	1 (0.5) [1]	1 (0.7) [1]	0	0	0	0	0
Skin infection	**2 (1.1) [2] {0.3}**	1 (0.5) [1]	0	1 (0.9) [1]	0	0	0	0
Gastroenteritis	**2 (1.1) [2] {0.3}**	0	0	1 (0.9) [1]	1 (1.1) [1]	0	0	0
Infection	**2 (1.1) [2] {0.3}**	0	1 (0.7) [1]	1 (0.9) [1]	0	0	0	0
Bronchitis	**4 (2.1) [5] {0.7}**	0	1 (0.7) [1]	1 (0.9) [1]	2 (2.2) [2]	0	1 (2.3) [1]	0
Viral infection	**2 (1.1) [2] {0.3}**	0	1 (0.7) [1]	0	0	1 (1.6) [1]	0	0
Gingivitis	**2 (1.1) [3] {0.4}**	0	1 (0.7) [1]	0	0	1 (1.6) [1]	1 (2.3) [1]	0
Viral upper respiratory tract infection	**2 (1.1) [2] {0.3}**	0	0	1 (0.9) [1]	0	1 (1.6) [1]	0	0

[#]=number of individual occurrences of the TEAE within the SOC/PT category and cycle; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAE within the SOC/PT category and cycle; N==number of study participants treated with the dose at least once; PT=preferred term; RLZ=rozanolixizumab; SOC=system organ class; TEAE=treatment-emergent adverse event Note: Summaries by Cycle are displayed if the total number of study participants undergoing the Cycle in RLZ Total was ≥10. Note: Summary data and the 100ER in the 'Sum of Cycles' column are derived from a 'most recent dose' analysis. Data for each individual Cycle are derived from a 'by Cycle' analysis. Therefore, the number of events presented by Cycle may not equal the number of events occurring in All Cycles.

Serious infections

Serious TEAEs within the SOC Infections and infestations occurred in 8 (4.3%) participants in Pool S2 (N=188), including 2 (1.5%) and 6 (4.6%) participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. The most common serious TEAE within this SOC was COVID-19 (3 [1.6%] of participants). There was no increase in serious infections with repeated cyclic treatment. Of the 8 participants with serious infections, 3 participants had fatal outcomes, and 5 participants (with 6 events) fully recovered from the event. There were 2 events that were considered related to rozanolixizumab by the Sponsor: a fatal event of severe pneumonia and aseptic meningitis.

Aseptic meningitis

There have been 3 reports of aseptic meningitis (reported as drug-induced aseptic meningitis) in the rozanolixizumab development programme, including 1 case in the ongoing OLE MG0007 and 2 cases in another indication.

Opportunistic infections

A MedDRA SMQ search for opportunistic infections (narrow search) found no events in Pool S2.

Hypersensitivity reactions

Placebo-controlled study (MG0003)

Anaphylactic reactions: No TEAEs met criteria for potential anaphylactic reactions.

Hypersensitivity: Treatment-emergent AEs mapping to the SMQ hypersensitivity occurred in 7 (10.9%), 4 (5.8%), and 1 (1.5%) participant in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. The most common event was rash (Table 84). All events were mild or moderate in intensity. There were no severe or serious events.

Table 84: Incidence of treatment-emergent AEs of focus modified analysis set: Safety Set. Hypersensitivity reactions.

MedDRA 24.0 System Organ Class High Level Term Preferred Term	Placebo N=67 n (%) [#]	RLZ ~7mg/kg N=64 n (%) [#]	RLZ ~10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any Hypersensitivity reaction	1 (1.5) [1]	7 (10.9) [8]	4 (5.8) [4]	11 (8.3) [12]
Gastrointestinal disorders	0	1 (1.6) [2]	0	1 (0.8) [2]
Tongue signs and symptoms	0	1 (1.6) [2]	0	1 (0.8) [2]
Swollen tongue	0	1 (1.6) [2]	0	1 (0.8) [2]
General disorders and administration site conditions	1 (1.5) [1]	2 (3.1) [2]	0	2 (1.5) [2]
Injection site reactions	1 (1.5) [1]	2 (3.1) [2]	0	2 (1.5) [2]
Injection site rash	0	2 (3.1) [2]	0	2 (1.5) [2]
Injection site urticaria	1 (1.5) [1]	0	0	0
Skin and subcutaneous tissue disorders	0	4 (6.3) [4]	4 (5.8) [4]	8 (6.0) [8]
Dermatitis and eczema	0	1 (1.6) [1]	0	1 (0.8) [1]
Eczema	0	1 (1.6) [1]	0	1 (0.8) [1]
Rashes, eruptions and exanthems NEC	0	3 (4.7) [3]	4 (5.8) [4]	7 (5.3) [7]
Rash	0	3 (4.7) [3]	3 (4.3) [3]	6 (4.5) [6]
Rash erythematous	0	0	1 (1.4) [1]	1 (0.8) [1]

~=equivalent dose, MedDRA=Medical Dictionary for Regulatory Activities, RLZ=Rozanolixizumab, AEOF=Adverse events of focus, TEAE=Treatment-Emergent Adverse Event
Note: n=number of participants reporting at least one AEOF within System Organ Class/High Level Group Term/High Level Term/Preferred Term
Note: [#] is the number of individual occurrences of the AEOF
Note: Selection criteria of AEOFs is specified in modified AEOF document after SAP finalisation.

Injection site reactions: Injection site reactions occurred in 4 (6.3%), 4 (5.8%), and 2 (3.0%) study participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg group, and placebo groups, respectively. All TEAEs in this category were mild. No study participants experienced serious TEAEs.

Table 85: Incidence of treatment-emergent AEs of focus modified analysis set: Safety Set. Injection site reactions.

MedDRA 24.0 System Organ Class High Level Term Preferred Term	Placebo N=67 n (%) [#]	RLZ ~7mg/kg N=64 n (%) [#]	RLZ ~10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any Injection site reaction	2 (3.0) [2]	4 (6.3) [6]	4 (5.8) [5]	8 (6.0) [11]
General disorders and administration site conditions	2 (3.0) [2]	4 (6.3) [6]	4 (5.8) [5]	8 (6.0) [11]
Administration site reactions NEC	0	0	1 (1.4) [1]	1 (0.8) [1]
Vessel puncture site bruise	0	0	1 (1.4) [1]	1 (0.8) [1]
Infusion site reactions	1 (1.5) [1]	1 (1.6) [1]	3 (4.3) [3]	4 (3.0) [4]
Infusion site erythema	0	1 (1.6) [1]	1 (1.4) [1]	2 (1.5) [2]
Infusion site bruising	1 (1.5) [1]	0	1 (1.4) [1]	1 (0.8) [1]
Infusion site pain	0	0	1 (1.4) [1]	1 (0.8) [1]
Injection site reactions	1 (1.5) [1]	4 (6.3) [5]	1 (1.4) [1]	5 (3.8) [6]
Injection site rash	0	2 (3.1) [2]	0	2 (1.5) [2]
Injection site discomfort	0	0	1 (1.4) [1]	1 (0.8) [1]
Injection site erythema	0	1 (1.6) [1]	0	1 (0.8) [1]
Injection site inflammation	0	1 (1.6) [1]	0	1 (0.8) [1]
Injection site reaction	0	1 (1.6) [1]	0	1 (0.8) [1]
Injection site urticaria	1 (1.5) [1]	0	0	0

~=equivalent dose, MedDRA=Medical Dictionary for Regulatory Activities, RLZ=Rozanolixizumab, AEOF=Adverse events of focus, TEAE=Treatment-Emergent Adverse Event
Note: n=number of participants reporting at least one AEOF within System Organ Class/High Level Group Term/High Level Term/Preferred Term
Note: [#] is the number of individual occurrences of the AEOF

Note: Selection criteria of AEOFs is specified in modified AEOF document after SAP finalisation.

Pool S2

Anaphylactic reactions

There were no events that met the defined search for anaphylactic reactions in Pool S2.

Hypersensitivity

In Pool S2 (N=188), the incidence of TEAEs mapping to the SMQ hypersensitivity was low, occurring in 25 (13.3%) study participants, including 14 (10.5%) and 11 (8.4%) participants, in the rozanolixizumab ≈7mg/kg (N=133) and ≈10mg/kg (N=131) dose groups, respectively. Excluding injection site reactions (which are discussed below), common TEAEs were rash (11 [5.9%] participants) and urticaria (3 [1.6%]). Hypersensitivity-related TEAEs were all nonserious and except for severe rash in 1 (0.5%) participant were of mild to moderate intensity. This participant with severe rash was subsequently diagnosed with SCLE. There were no hypersensitivity TEAEs that led to permanent discontinuation. Overall, the incidence of TEAEs by Cycle did not increase with repeated cyclic treatment (<7% of participants per Cycle).

Injection site reactions

In total, 23 (12.2%) study participants experienced an injection site reaction in Pool S2 (N=188), with the incidence similar across the ≈7mg/kg (N=133) and ≈10mg/kg (N=131) dose groups (13 [9.8%] and 12 [9.2%] participants, respectively). Injection site reactions occurring in >3 participants were injection site erythema in 5 (2.7%) participants, injection site bruising in 4 (2.1%) participants, and injection site rash in 4 (2.1%) participants. All injection site reactions were non-serious, mild to moderate in intensity, and did not lead to discontinuation. By Cycle, the incidence of injection site reactions did not increase with repeated cyclic treatment (≤7% of participants per Cycle).

Gastrointestinal disturbances

Placebo-controlled study (MG0003)

Treatment-emergent AEs meeting the search criteria for GI disturbances occurred in 20 (31.3%), 19 (27.5%), and 13 (19.4%) participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. The most common TEAEs in the rozanolixizumab groups compared with the placebo group were diarrhoea, nausea, and vomiting (Table 74).

With the exception of severe vomiting in 1 (1.6%) participant in the rozanolixizumab ≈7mg/kg group and severe diarrhoea in 2 (2.9%) participants in the ≈10mg/kg group, all events were of mild or moderate intensity. For 2 (3.1%) participants in the rozanolixizumab ≈7mg/kg group, the GI events (gastritis and vomiting) were serious. Discontinuations from the study due to GI disturbances occurred in 2 (2.9%) study participants in the rozanolixizumab ≈10mg/kg group (vomiting and abdominal pain upper in 1 participant; diarrhoea in 1 participant).

Table 86: Incidence of treatment-emergent AEs of focus modified analysis set: Safety Set. GI disturbances.

MedDRA 24.0 System Organ Class High Level Term Preferred Term	Placebo N=67 n (%) [#]	RLZ ~7mg/kg N=64 n (%) [#]	RLZ ~10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any Gastrointestinal disturbance	13 (19.4) [36]	20 (31.3) [37]	19 (27.5) [35]	39 (29.3) [72]
Gastrointestinal disorders	13 (19.4) [36]	20 (31.3) [37]	19 (27.5) [35]	39 (29.3) [72]
Diarrhoea (excl infective)	9 (13.4) [14]	16 (25.0) [18]	11 (15.9) [18]	27 (20.3) [36]
Diarrhoea	9 (13.4) [14]	16 (25.0) [18]	11 (15.9) [18]	27 (20.3) [36]
Gastritis (excl infective)	0	1 (1.6) [1]	0	1 (0.8) [1]
Gastritis	0	1 (1.6) [1]	0	1 (0.8) [1]
Gastrointestinal and abdominal pains (excl oral and throat)	4 (6.0) [6]	3 (4.7) [3]	4 (5.8) [4]	7 (5.3) [7]
Abdominal pain upper	2 (3.0) [4]	3 (4.7) [3]	2 (2.9) [2]	5 (3.8) [5]
Abdominal pain	2 (3.0) [2]	0	2 (2.9) [2]	2 (1.5) [2]
Gastrointestinal signs and symptoms NEC	0	2 (3.1) [4]	1 (1.4) [1]	3 (2.3) [5]
Abdominal discomfort	0	2 (3.1) [4]	1 (1.4) [1]	3 (2.3) [5]
Nausea and vomiting symptoms	5 (7.5) [16]	6 (9.4) [11]	12 (17.4) [12]	18 (13.5) [23]
Nausea	5 (7.5) [12]	5 (7.8) [7]	8 (11.6) [8]	13 (9.8) [15]
Vomiting	1 (1.5) [4]	2 (3.1) [4]	4 (5.8) [4]	6 (4.5) [8]

~=equivalent dose, MedDRA=Medical Dictionary for Regulatory Activities, RLZ=Rozanolixizumab, AEOF=Adverse events of focus, TEAE=Treatment-Emergent Adverse Event
Note: n=number of participants reporting at least one AEOF within System Organ Class/High Level Group Term/High Level Term/Preferred Term
Note: [#] is the number of individual occurrences of the AEOF
Note: Selection criteria of AEOFs is specified in modified AEOF document after SAP finalisation.

Pool S2

In total, 73 (38.8%) study participants experienced any GI disturbance in Pool S2 (N=188), with the incidence similar across the ≈7mg/kg (N=133) and ≈10mg/kg (N=131) dose groups (38 [28.6%] and 48 [36.6%] participants, respectively), and higher during the Treatment Period compared with the Follow-up Period. The most common TEAEs meeting criteria for GI disturbances were diarrhoea, nausea, and abdominal pain. Compared with Cycle 1, the incidence of any GI disturbance did not increase with repeated cyclic treatment.

In total, 2 (1.1%) participants had a serious GI disturbance (gastritis and vomiting), both in the rozanolixizumab ≈7mg/kg group, and in total 3 (1.6%) participants had severe GI disturbances in either the ≈7mg/kg group (vomiting in 1 participant [0.8%]) or ≈10mg/kg group (diarrhoea in 2 participants [1.5%]).

Hepatic events

Placebo-controlled study (MG0003)

Treatment-emergent AEs meeting the search criteria for drug-related hepatic disorders were reported in 1 (1.6%) study participant in the rozanolixizumab ≈7mg/kg group, 4 (5.8%) in the ≈10mg/kg group, and 1 (1.5%) in the placebo group. The following PTs were reported: hepatic fibrosis, blood bilirubin increased, prothrombin time prolonged, transaminases increased, and non-alcoholic fatty liver disease. None of these events were reported in >1 study participant in any treatment group except for blood bilirubin increased which was reported in 2 (2.9%) study participants in the rozanolixizumab ≈10mg/kg group.

All events were mild or moderate in intensity and there were no serious events or events that led to discontinuation from the study.

Table 87: Incidence of treatment-emergent AEs of focus modified analysis set: Safety Set. Drug-related hepatic disorders

MedDRA 24.0 System Organ Class High Level Term Preferred Term	Placebo N=67 n (%) [#]	RLZ ~7mg/kg N=64 n (%) [#]	RLZ ~10mg/kg N=69 n (%) [#]	RLZ Total N=133 n (%) [#]
Any Drug related hepatic disorder	1 (1.5) [1]	1 (1.6) [2]	4 (5.8) [4]	5 (3.8) [6]
Hepatobiliary disorders	1 (1.5) [1]	1 (1.6) [2]	0	1 (0.8) [2]
Hepatic fibrosis and cirrhosis	0	1 (1.6) [1]	0	1 (0.8) [1]
Hepatic fibrosis	0	1 (1.6) [1]	0	1 (0.8) [1]
Hepatocellular damage and hepatitis NEC	1 (1.5) [1]	1 (1.6) [1]	0	1 (0.8) [1]
Nonalcoholic fatty liver disease	1 (1.5) [1]	1 (1.6) [1]	0	1 (0.8) [1]
Investigations	0	0	4 (5.8) [4]	4 (3.0) [4]
Coagulation and bleeding analyses	0	0	1 (1.4) [1]	1 (0.8) [1]
Prothrombin time prolonged	0	0	1 (1.4) [1]	1 (0.8) [1]
Liver function analyses	0	0	3 (4.3) [3]	3 (2.3) [3]
Blood bilirubin increased	0	0	2 (2.9) [2]	2 (1.5) [2]
Transaminases increased	0	0	1 (1.4) [1]	1 (0.8) [1]

~=equivalent dose, MedDRA=Medical Dictionary for Regulatory Activities, RLZ=Rozanolixizumab, AEOF=Adverse events of focus, TEAE=Treatment-Emergent Adverse Event
Note: n=number of participants reporting at least one AEOF within System Organ Class/High Level Group Term/High Level Term/Preferred Term
Note: [#] is the number of individual occurrences of the AEOF
Note: Selection criteria of AEOFs is specified in modified AEOF document after SAP finalisation.

Pool S2

In total, 9 (4.8%) study participants had 13 TEAEs that met search criteria for drug-related hepatic disorders in Pool S2 (N=188), including 2 (1.5%) participants in the ≈7mg/kg dose group (3 events) and 7 (5.3%) in the ≈10mg/kg dose group (10 events). There were no serious TEAEs and 1 severe TEAE. None of the TEAEs occurred in >2 (1.1%) participants. By Cycle, the incidence of any drug-related hepatic disorders did not increase with repeated cyclic treatment.

One of the TEAEs of LFT increase in the rozanolixizumab ≈10mg/kg group resulted in study discontinuation.

Effects on the kidney

Placebo-controlled study (MG0003)

Treatment-emergent AEs meeting criteria for effects on the kidney comprised of renal impairment in 3 (4.3%) participants in the rozanolixizumab ≈10mg/kg group. No study participants had severe or serious TEAEs of renal impairment. All 3 participants had pre-existing medical conditions and/or low eGFR at the baseline.

Pool S2

There were no additional participants with TEAEs related to effects on the kidney beyond the 3 (1.6%) participants who reported events in MG0003.

2.6.8.4. Laboratory findings

Haematology

Placebo-controlled study (MG0003)

In general, the mean values for the haematology parameters remained stable over time. Decreases from Baseline in mean and median neutrophils levels during the Treatment Period were observed in the

rozanolixizumab treatment groups compared with placebo; levels returned to Baseline by Day 99, ie, by end of Observation Period.

In MG0003, a similar proportion of study participants had MA low lymphocytes values (<0.5x10^9/L) in the rozanolixizumab ≈7mg/kg (4 [6.3%]), ≈10mg/kg (7 [10.1%]), and placebo (8 [11.9%]) groups. Markedly abnormal low leukocytes (<2x10^9/L) and neutrophils (<1x109/L) occurred in 1 (1.6%) study participant in the ≈7mg/kg group and 1 (1.4%) study participant in the ≈10mg/kg group, respectively, and in none of the participants in the placebo group. One participant in placebo (1.5%) and 1 participant in ≈10mg/kg (1.4%) had MA low haemoglobin (<80g/L).

Open-label extension study (MG0007)

In general, the mean values for the haematology laboratory results remained stable over time. No clinically relevant trends in haematology laboratory data shifts were identified with repeated cyclic treatment.

Individual clinically relevant abnormalities

In Pool S2 (N=188), the total incidence of TEAEs related to haematology abnormalities is low and comprised of lymphopenia (3 [1.6%] participants), lymphocyte count decreased (8 [4.3%]), neutrophil count decreased, neutrophil count increased (both 2 [1.1%] each), and white blood cell count decreased (1 [0.5%]). The only events that were assessed as severe or led to temporary withdrawal of IMP were lymphopenia (2 [1.1%] and 1 [0.5%] participants, respectively) and lymphocyte count decreased (both 1 [0.5%]), all occurring in the rozanolixizumab ≈10mg/kg dose group. Except for 4 participants, all participants with a TEAE related to lymphocyte count were receiving concomitant azathioprine.

Change from baseline in platelet count

Across the rozanolixizumab development programme, reductions in platelets counts without clinical consequences have been observed following rozanolixizumab administration, with evidence of positive dechallenge and rechallenge.

In MG0003, the incidence of normal to low shifts from Baseline in platelet levels was similar in the placebo group (5 [7.5%] participants) compared with the rozanolixizumab ≈7mg/kg (2 [3.1%] participants) and ≈10mg/kg (2 [2.9%] participants) groups. The largest median changes from Baseline occurred at Day 8 in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups (-16.0x10^9/L, range -104 to 140x10^9/L and -16.0 x10^9/L, range -262 to 202x10^9/L, respectively) and, except for Day 22, were greater than placebo (Day 8 median change from Baseline -8.0x10^9/L, range -188 to 69x10^9/L) at each visit of the Treatment Period. By the end of the Observation Period, platelets had returned to at least Baseline levels.

With repeated cyclic treatment in MG0007, median decreases in platelet count were generally similar to that observed in MG0003.

With chronic treatment in MG0004, the largest median reductions occurred at Week 9 in the rozanolixizumab ≈7mg/kg (N=25) treatment arm (-37.0x10^9/L, range -144 to 66x10^9/L) and at Week 29 (N=7) in the ≈10mg/kg treatment arm (-74.0x10^9/L, range -216 to 29x10^9/L).

There were no participants with MA low (<50x10^9/L) platelet count values post baseline. Only 1 participant reported mild thrombocytopenia on Day 10 while receiving rozanolixizumab ≈7mg/kg, and on Day 20 while receiving rozanolixizumab ≈7mg/kg in MG0004. No TEAE related to thrombocytopenia was reported in MG0007.

Clinical chemistry

Placebo-controlled study (MG0003)

In general, the mean values for the clinical chemistry parameters remained stable over time. Slight increases from Baseline in mean C-reactive protein levels over time were observed in the rozanolixizumab treatment groups (especially the ≈10mg/kg) compared with placebo.

There were no notable clinical chemistry laboratory data shifts other than the higher frequency of shifts from normal to low in protein levels in both rozanolixizumab treatment groups compared with placebo and the higher proportion of shifts from normal to high in CRP in the rozanolixizumab ≈10mg/kg group (28 participants [40.6%]) compared with rozanolixizumab ≈7mg/kg (10 participants [15.6%]) and placebo (9 participants [13.4%]) groups.

Open-label extension study (MG0007)

In general, the mean values for the clinical chemistry parameters remained stable over time. No clinically relevant trends in clinical chemistry laboratory data shifts were identified with repeated cyclic treatment.

Liver function test elevations

There have been no cases of potential Hy's Law in the rozanolixizumab development programme, thus no participants have met criteria for this adverse events of special interest (AESI). None of the participants in the rozanolixizumab development programme have met drug induced liver injury criteria.

Overall, an assessment of hepatic events and abnormal liver function tests did not indicate a potential of rozanolixizumab to cause hepatotoxicity or drug induced liver injury.

Change from baseline in lipid panels

Placebo-controlled study (MG0003)

Lipid laboratory data were available for approximately half of the study participants. No clinically meaningful changes from Baseline at Day 43 or Day 99 were observed in non-fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides levels in any treatment group. The mean (SD) change from Baseline in LDL cholesterol levels at Day 43 was 0.023 (0.481) mmol/L in the rozanolixizumab ≈7mg/kg group, -0.190 (0.907) mmol/L in the ≈10mg/kg group, and -0.080 (0.703) mmol/L in the placebo group. There were no TEAEs related to lipid abnormalities in MG0003.

Open-label extension study (MG0007)

In general, the mean values for the lipid parameters remained stable over time. The occurrence of individual shifts from normal at Baseline to either low or high values was low. No clinically relevant trends in lipid laboratory data shifts were identified with repeated cyclic treatment.

Albumin and total protein

Placebo-controlled study (MG0003)

Slight reductions in mean albumin levels were observed at all timepoints for both rozanolixizumab treatment groups; however, the reductions were not clinically significant. The maximum mean change from Baseline in albumin levels was -2.6g/L (at Day 36) and -2.4g/L (at Day 36 and Day 43) for the rozanolixizumab ≈7mg/kg and ≈10mg/kg groups, respectively, compared with -1.1g/L at Day 36 for the placebo group.

Open-label extension study (MG0007)

Decreases from Baseline in mean total protein levels occurred in both rozanolixizumab treatment groups during the Treatment Period and ranged between -8.0g/L (Cycle 1, Day 36) and –4.3g/L (Cycle 5, Day 43) in the ≈7mg/kg group and between -8.7g/L (Cycle 7, Day 15) and –4.1g/L (Cycle 5, Day 15) in the ≈10mg/kg group. These decreases in total protein levels are consistent with the mechanism of action of rozanolixizumab and driven primarily by reductions in IgG levels.

Minimal reductions (up to ~5%) from Baseline in albumin levels during the Treatment Period in both rozanolixizumab treatment groups were not considered clinically meaningful.

Pooled data

No study participants experienced TEAEs meeting the described criteria.

Urinalysis

Placebo-controlled study (MG0003)

In general, mean urinalysis values remained stable over time. There were no notable urinalysis laboratory data shifts from normal at Baseline.

Open-label extension study (MG0007)

In general, mean values remained stable over time. There were no notable urinalysis laboratory data shifts from normal at Baseline to high or low post- Baseline. Six TEAEs (all non-serious, mild, and assessed as not related to rozanolixizumab) were reported in MG0007: In the ≈7mg/kg group, microalbuminuria and albumin urine were both reported in the same participant (1.0%), and in the ≈10mg/kg group glycosuria, haematuria, glucose urine present, and protein urine present were reported in 1 (1.0%) participant each.

Vital signs and electrocardiograms

Placebo-controlled study (MG0003)

Overall, mean vital sign (systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate, respiratory rate, and temperature) measurements remained stable over time. There were no shifts from Baseline in 12-lead ECG interpretation to abnormal clinically significant postbaseline.

The incidence of markedly abnormal vital sign values was low, and similar between treatment groups. The frequency of markedly abnormal ECG values was low and there were no imbalances between treatment groups. None of the participants had a QT interval or QTcF interval ≥500msec, or an increase from Baseline in QTcF interval of ≥60msec. Given the duration of exposure and frequency of assessments, there was no increase of abnormal findings over time.

Open-label extension study (MG0007)

Overall, mean vital sign measurements signs (SBP and DBP, pulse rate, and temperature) remained stable over time. Slight reductions from Baseline were observed in mean systolic BP in Cycles 1, 2, 3, and 4 with subsequent recovery that were not dose-dependent and were not considered clinically meaningful.

Overall, mean 12-lead ECG parameters remained stable over time. There were no shifts from normal at Baseline to abnormal clinically significant values. There was 1 shift from abnormal not clinically significant at Baseline to abnormal clinically significant, which occurred in a study participant in the rozanolixizumab ≈7mg/kg group in Cycle 2.

Individual clinically relevant abnormalities

Treatment-emergent AEs potentially related to abnormal vital sign values in Pool S2 were hyperthermia (1 [0.5%] participant), hypertension (12 [6.4%]), hypotension (3 [1.6%]), oxygen saturation decreased (1 [0.5%]), body temperature increased (2 [1.1%]), and pyrexia (34 [18.1%]). Treatment-emergent AEs potentially related to abnormal ECG values (palpitations, tachycardia, and BP increased) were of low incidence (≤2 (1.1%) participants per TEAE) and showed no association with Cycle.

Assessment of suicidality

Placebo-controlled study (MG0003)

In MG0003, study participants underwent a query for suicidality which was accompanied by a full C-SSRS assessment in the event a study participant answered 'yes' to Question 1 of the suicidal ideation query. No noteworthy C-SSRS suicidality findings were reported.

Open-label extension study (MG0007)

None of the 4 study participants who responded 'yes' to Question 1 of the Columbia-Suicide Severity Rating Scale had active suicidal ideation meeting withdrawal criteria. One of these participants decided to withdraw from the study due to personal reasons.

2.6.8.5. In vitro biomarker test for patient selection for safety

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

2.6.8.6. Safety in special populations

Safety by administered fixed dose

Across the 4 body weight tiers, the 5 different fixed doses ≈7mg/kg or ≈10mg/kg administered in MG0003, MG0007, and MG0004 were 280mg, 420mg, 560mg, 840mg, and 1120mg. For MG0003, MG0007 (Table 88), and MG0004, there was variability in the number of participants receiving each of the fixed doses, with the lowest number of participants receiving the 280mg fixed dose.

Table 88: MG0003 and MG0007: Overview of TEAEs by administered dose (SS)

Category	MG0003						MG0007				
		RLZ administered dose					RLZ administered dose				
	Placebo N=67 n (%) [#]	280mg N=7 n (%) [#]	420mg N=19 n (%) [#]	560mg N=53 n (%) [#]	840mg N=35 n (%) [#]	1120mg N=19 n (%) [#]	280mg N=5 n (%) [#]	420mg N=34 n (%) [#]	560mg N=72 n (%) [#]	840mg N=58 n (%) [#]	1120mg N=25 n (%) [#]
Any TEAEs	45 (67.2) [191]	6 (85.7) [15]	15 (78.9) [79]	46 (86.8) [191]	25 (71.4) [94]	17 (89.5) [95]	2 (40.0) [27]	23 (67.6) [122]	55 (76.4) [423]	52 (89.7) [320]	22 (88.0) [158]
Serious TEAEs	6 (9.0) [6]	0	2 (10.5) [3]	4 (7.5) [4]	3 (8.6) [4]	3 (15.8) [4]	0	2 (5.9) [2]	11 (15.3) [16]	13 (22.4) [16]	5 (20.0) [7]
Participant discontinuation from study due to TEAEs	2 (3.0) [2]	0	1 (5.3) [1]	3 (5.7) [4]	2 (5.7) [2]	1 (5.3) [1]	0	1 (2.9) [1]	8 (11.1) [11]	10 (17.2) [10]	3 (12.0) [3]
Permanent discontinuation of IMP due to TEAEs	2 (3.0) [2]	0	1 (5.3) [1]	3 (5.7) [6]	2 (5.7) [2]	0	0	1 (2.9) [1]	8 (11.1) [11]	10 (17.2) [10]	2 (8.0) [2]
Temporary discontinuation of IMP due to TEAEs	1 (1.5) [1]	0	0	2 (3.8) [2]	4 (11.4) [5]	3 (15.8) [3]	0	4 (11.8) [7]	12 (16.7) [19]	9 (15.5) [20]	3 (12.0) [10]
TEAEs requiring dose change	NR	NR	NR	NR	NR	NR	0	0	1 (1.4) [1]	0	0
Treatment-related TEAEs	22 (32.8) [94]	3 (42.9) [8]	10 (52.6) [36]	32 (60.4) [87]	16 (45.7) [61]	10 (52.6) [37]	2 (40.0) [21]	7 (20.6) [39]	39 (54.2) [188]	28 (48.3) [141]	14 (56.0) [53]
Severe TEAEs[a]	3 (4.5) [3]	0	1 (5.3) [1]	6 (11.3) [8]	7 (20.0) [8]	2 (10.5) [3]	1 (20.0) [1]	1 (2.9) [1]	12 (16.7) [22]	16 (27.6) [22]	5 (20.0) [10]
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0	0	2 (3.4) [2]	1 (4.0) [1]
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	2 (3.4) [2]	1 (4.0) [1]

[#]=number of individual occurrences of the TEAE in that category; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: "All deaths" is based on all study participants screened and refers to all deaths occurring on study.
Note: For subgroup categories of AEs, percentages are based on the total number of study participants in the subgroup category within each treatment group.
a Severe TEAEs are those with CTCAE Grade 3 or above, or those with "severe" intensity as assessed by the investigator

Sex

In MG0003 and Pool S2, there were no clear trends in the incidences of TEAE categories by sex subgroup (Table 89). The only notable difference was the higher incidence of treatment-related TEAEs in female compared with male participants in both rozanolixizumab-treated participants in MG0003 (59.5% vs 45.8%) and Pool S2 (63.1% vs 53.2%).

Table 89: MG0003 (SS) and Pool S2: Overview of TEAEs by sex subgroup

Category	MG0003				Pool S2	
	Placebo N=67 n (%) [#]		RLZ Total N=133 n (%) [#]		RLZ Total N=188 n (%) [#] {100ER}	
	Male	Female	Male	Female	Male	Female
	n=20	n=47	n=59	n=74	n=77 Sum of Cycles=271	n=111 Sum of Cycles=407
Any TEAEs	12 (60.0) [37]	33 (70.2) [154]	47 (79.7) [187]	62 (83.8) [287]	71 (92.2) [570] {210.3}	98 (88.3) [956] {234.9}
Serious TEAEs	0	6 (12.8) [6]	6 (10.2) [8]	6 (8.1) [7]	20 (26.0) [27] {10.0}	22 (19.8) [29] {7.1}
Participant discontinuation from study due to TEAEs	0	2 (4.3) [2]	2 (3.4) [2]	5 (6.8) [6]	11 (14.3) [12] {4.4}	18 (16.2) [21] {5.2}
Permanent discontinuation of IMP due to TEAEs	0	2 (4.3) [2]	1 (1.7) [1]	5 (6.8) [8]	9 (11.7) [10] {3.7}	18 (16.2) [23] {5.7}
Temporary discontinuation of IMP due to TEAEs	0	1 (2.1) [1]	7 (11.9) [8]	2 (2.7) [2]	14 (18.2) [34] {12.5}	18 (16.2) [32] {7.9}
Treatment-related TEAEs	6 (30.0) [9]	16 (34.0) [85]	27 (45.8) [72]	44 (59.5) [157]	41 (53.2) [197] {72.7}	70 (63.1) [475] {116.7}
Severe TEAEs[a]	0	3 (6.4) [3]	7 (11.9) [9]	9 (12.2) [11]	21 (27.3) [31] {11.4}	29 (26.1) [45] {11.1}
Deaths (TEAEs leading to death)	0	0	0	0	2 (2.6) [2] {0.7}	1 (0.9) [1] {0.2}

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=number of study participants with exposure to the respective dose; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event.
a Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator.

Age

In Pool S2 there were no clear trends in the incidences of TEAE categories by age subgroup with the exception of the higher incidence of treatment-related TEAEs in the younger population MG0003 (62 [62.0%] vs 9 [27.3%]) and Pool S2 (87 [62.1%] vs 24 [50.0%]) (Table 90).

Table 90: MG0003 (SS) and Pool S2: Overview of TEAEs by age subgroup

Category	MG0003				Pool S2	
	Placebo N=67 n (%) [#]		RLZ Total N=133 n (%) [#]		RLZ Total N=188 n (%) [#] {100ER}	
	18 to <65 years	≥65 years	18 to <65 years	≥65 years	18 to <65 years	≥65 years
	n=51	n=16	n=100	n=33	n=140 Sum of Cycles=522	n=48 Sum of Cycles=156
Any TEAEs	31 (60.8) [138]	14 (87.5) [53]	85 (85.0) [377]	24 (72.7) [97]	127 (90.7) [1121] {214.8}	42 (87.5) [405] {259.6}
Serious TEAEs	4 (7.8) [4]	2 (12.5) [2]	10 (10.0) [12]	2 (6.1) [3]	29 (20.7) [39] {7.5}	13 (27.1) [17] {10.9}
Participant discontinuation from study due to TEAEs	2 (3.9) [2]	0	5 (5.0) [6]	2 (6.1) [2]	20 (14.3) [24] {4.6}	9 (18.8) [9] {5.8}
Permanent discontinuation of IMP due to TEAEs	2 (3.9) [2]	0	5 (5.0) [8]	1 (3.0) [1]	19 (13.6) [25] {4.8}	8 (16.7) [8] {5.1}
Temporary discontinuation of IMP due to TEAEs	1 (2.0) [1]	0	6 (6.0) [7]	3 (9.1) [3]	21 (15.0) [47] {9.0}	11 (22.9) [19] {12.2}
Treatment-related TEAEs	16 (31.4) [81]	6 (37.5) [13]	62 (62.0) [211]	9 (27.3) [18]	87 (62.1) [527] {101.0}	24 (50.0) [145] {92.9}
Severe TEAEs[a]	3 (5.9) [3]	0	14 (14.0) [17]	2 (6.1) [3]	34 (24.3) [46] {8.8}	16 (33.3) [30] {19.2}
Deaths (TEAEs leading to death)	0	0	0	0	2 (1.4) [2] {0.4}	1 (2.1) [1] {0.6}

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=number of study participants with exposure to the respective dose; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event. a Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator.

Weight

In MG0003, there were no clear trends in the incidences of TEAE categories by weight subgroup (Table 91); although interpretation is limited by the low number of participants in the <50kg subgroup in both studies and the variability in the data.

In MG0007, across TEAE categories the incidence of TEAEs was higher in the 70kg to 100kg weight group. There was no overall trend for increasing incidence by weight, as an increased incidence was not observed in the highest weight group (≥100kg). By Cycle, for the 70kg to 100kg weight group there was a high variability in the distribution of TEAEs between the 560mg and 840mg dose groups.

Table 91: MG0003 and MG0007: Overview of TEAEs by weight subgroup (SS)

Category	MG0003								MG0007			
	Placebo N=67 n (%) [#]				RLZ Total N=133 n (%) [#]				RLZ Total N=157 n (%) [#]			
	<50kg N=4	≥50kg to <70kg N=16	≥70kg to <100kg N=35	≥100kg N=12	<50kg N=8	≥50kg to <70kg N=45	≥70kg to <100kg n=48	≥100kg n=32	<50kg N=10	≥50kg to <70kg N=46	≥70kg to <100kg N=65	≥100kg N=36
Any TEAEs	2 (50.0) [3]	13 (81.3) [54]	21 (60.0) [104]	9 (75.0) [30]	7 (87.5) [20]	38 (84.4) [171]	37 (77.1) [163]	27 (84.4) [120]	8 (80.0) [60]	38 (82.6) [312]	55 (84.6) [424]	32 (88.9) [256]
Serious TEAEs	0	2 (12.5) [2]	3 (8.6) [3]	1 (8.3) [1]	0	5 (11.1) [6]	2 (4.2) [2]	5 (15.6) [7]	1 (10.0) [1]	6 (13.0) [7]	16 (24.6) [24]	7 (19.4) [9]
Participant discontinuation from study due to TEAEs	0	2 (12.5) [2]	0	0	0	4 (8.9) [5]	1 (2.1) [1]	2 (6.3) [2]	1 (10.0) [1]	4 (8.7) [4]	12 (18.5) [15]	5 (13.9) [5]
Permanent discontinuation of IMP due to TEAEs	0	2 (12.5) [2]	0	0	0	4 (8.9) [7]	1 (2.1) [1]	1 (3.1) [1]	1 (10.0) [1]	4 (8.7) [4]	12 (18.5) [15]	4 (11.1) [4]
Temporary discontinuation of IMP due to TEAEs	0	0	1 (2.9) [1]	0	0	1 (2.2) [1]	3 (6.3) [4]	5 (15.6) [5]	1 (10.0) [3]	5 (10.9) [7]	15 (23.1) [32]	4 (11.1) [14]
TEAEs requiring dose change	NC	NC	NC	NC	NC	NC	NC	NC	0	1 (2.2) [1]	0	0
Treatment-related TEAEs	0	5 (31.3) [31]	11 (31.4) [53]	6 (50.0) [10]	4 (50.0) [11]	27 (60.0) [86]	24 (50.0) [80]	16 (50.0) [52]	4 (40.0) [36]	22 (47.8) [138]	36 (55.4) [180]	17 (47.2) [89]
Severe TEAEs[a]	0	2 (12.5) [2]	1 (2.9) [1]	0	0	7 (15.6) [9]	5 (10.4) [5]	4 (12.5) [6]	2 (20.0) [2]	6 (13.0) [8]	19 (29.2) [34]	7 (19.4) [12]
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0	0	0	1 (1.5) [1]	2 (5.6) [2]
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	0	1 (1.5) [1]	2 (5.6) [2]

[#]=number of individual occurrences of the TEAE in that category; AE=adverse event; CTCAE= Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=total number of study participants in treatment group; NC=not calculated; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event. Note: "All deaths" is based on all participants screened and refers to all deaths occurring on study. a Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator

BMI

There was no impact of low BMI on the incidences of TEAE categories in either MG0003 or Pool S2 (Table 92); although interpretation is limited by the low number of participants receiving rozanolixizumab in the <18.5kg/m2 subgroup in both MG0003 (N=5) and Pool S2 (N=8).

Table 92: MG0003 (SS) and Pool S2: Overview of TEAEs by BMI subgroup

Category	MG0003 (SS)								Pool S2			
	Placebo N=67 n (%) [#]				RLZ Total N=133 n (%) [#]				RLZ Total N=188 n (%) [#] {100ER}			
	<18.5kg /m² N=4	≥18.5 to <25kg/ m² N=17	≥25 to <30kg/ m² N=21	≥30kg/ m² N=25	<18.5kg /m² N=5	≥18.5 to <25kg/ m² N=50	≥25 to <30kg/ m² N=31	≥30kg/ m² N=47	<18.5kg /m² N=8 Sum of Cycles= 33	≥18.5 to <25kg/ m² N=65 Sum of Cycles= 223	≥25 to <30kg/ m² N=47 Sum of Cycles= 196	≥30kg/ m² N=68 Sum of Cycles= 226
Any TEAEs	2 (50.0) [4]	14 (82.4) [68]	11 (52.4) [33]	18 (72.0) [86]	4 (80.0) [15]	40 (80.0) [143]	28 (90.3) [162]	37 (78.7) [154]	8 (100.0) [43] {130.3}	57 (87.7) [467] {209.4}	43 (91.5) [460] {234.7}	61 (89.7) [556] {246.0}
Serious TEAEs	1 (25.0) [1]	1 (5.9) [1]	1 (4.8) [1]	3 (12.0) [3]	1 (20.0) [1]	5 (10.0) [6]	3 (9.7) [3]	3 (6.4) [5]	2 (25.0) [2] {6.1}	10 (15.4) [12] {5.4}	14 (29.8) [21] {10.7}	16 (23.5) [21] {9.3}
Participant discontinuation from study due to TEAEs	1 (25.0) [1]	1 (5.9) [1]	0	0	0	4 (8.0) [5]	0	3 (6.4) [3]	0	10 (15.4) [11] {4.9}	6 (12.8) [8] {4.1}	13 (19.1) [14] {6.2}
Permanent discontinuation of IMP due to TEAEs	1 (25.0) [1]	1 (5.9) [1]	0	0	0	4 (8.0) [7]	0	2 (4.3) [2]	0	10 (15.4) [13] {5.8}	6 (12.8) [8] {4.1}	11 (16.2) [12] {5.3}
Temporary discontinuation of IMP due to TEAEs	0	0	1 (4.8) [1]	0	0	2 (4.0) [3]	4 (12.9) [4]	3 (6.4) [3]	1 (12.5) [1] {3.0}	6 (9.2) [10] {4.5}	13 (27.7) [32] {16.3}	12 (17.6) [23] {10.2}
Treatment-related TEAEs	0	7 (41.2) [47]	4 (19.0) [12]	11 (44.0) [35]	3 (60.0) [10]	29 (58.0) [80]	17 (54.8) [66]	22 (46.8) [73]	5 (62.5) [24] {72.4}	42 (64.6) [243] {109.0}	28 (59.6) [182] {92.9}	36 (52.9) [223] {98.7}
Severe TEAEs[a]	1 (25.0) [1]	1 (5.9) [1]	0	1 (4.0) [1]	1 (20.0) [1]	7 (14.0) [9]	2 (6.5) [2]	6 (12.8) [8]	2 (25.0) [2] {6.1}	16 (24.6) [21] {9.4}	11 (23.4) [22] {11.2}	21 (30.9) [31] {13.7}
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	0	0	3 (4.4) [3] {1.3}

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=number of study participants with exposure to the respective dose; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event a Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator

Race

The populations in both MG0003 and Pool S2 were predominantly in the White subgroup, therefore subgroup analysis by race is limited. Overall, there were no clear trends in the incidences of TEAE categories by race subgroup (Table 93).

Table 93: MG0003 (SS) and Pool S2: Overview of TEAEs by race subgroup

Category	MG0003						Pool S2		
	Placebo N=67[a] n (%) [#]			RLZ Total N=133[a] n (%) [#]			RLZ Total N=188[a] n (%) [#] {100ER}		
	Asian	Black	White	Asian	Black	White	Asian	Black	White
	n=5	n=1	n=46	n=16	n=4	n=90	n=21 Sum of Cycles=85	n=4 Sum of Cycles=10	n=127 Sum of Cycles=450
Any TEAEs	2 (40.0) [17]	0	32 (69.6) [140]	14 (87.5) [40]	3 (75.0) [24]	72 (80.0) [333]	20 (95.2) [195] {229.4}	3 (75.0) [28] {280.0}	114 (89.8) [1007] {223.8}
Serious TEAEs	0	0	5 (10.9) [5]	0	0	10 (11.1) [12]	3 (14.3) [3] {3.5}	0	33 (26.0) [45] {10.0}
Participant discontinuation from study due to TEAEs	0	0	2 (4.3) [2]	2 (12.5) [3]	0	4 (4.4) [4]	3 (14.3) [4] {4.7}	0	21 (16.5) [23] {5.1}
Permanent discontinuation of IMP due to TEAEs	0	0	2 (4.3) [2]	2 (12.5) [3]	0	3 (3.3) [5]	3 (14.3) [4] {4.7}	0	19 (15.0) [23] {5.1}
Temporary discontinuation of IMP due to TEAEs	0	0	0	0	0	8 (8.9) [9]	3 (14.3) [21] {24.7}	0	24 (18.9) [36] {8.0}
Treatment-related TEAEs	1 (20.0) [12]	0	13 (28.3) [60]	9 (56.3) [19]	3 (75.0) [14]	49 (54.4) [163]	15 (71.4) [105] {123.5}	3 (75.0) [14] {140.0}	75 (59.1) [433] {96.2}
Severe TEAEs[b]	0	0	3 (6.5) [3]	2 (12.5) [2]	1 (25.0) [1]	12 (13.3) [16]	6 (28.6) [6] {7.1}	1 (25.0) [1] {10.0}	36 (28.3) [58] {12.9}
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	3 (2.4) [3] {0.7}

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=number of study participants with exposure to the respective dose; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event

a In MG0003, the total N for placebo and RLZ dose groups includes study participants in the Native Hawaiian/Other Pacific Island (N=1 and 0, respectively), and Missing (N=14 and 23, respectively) categories. In Pool S2, the total N for RLZ includes study participants in the Native Hawaiian/Other Pacific Island (N=1) and Missing (N=35) categories.

b Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator

Renal impairment

The effect of renal impairment on the incidence of TEAE categories was evaluated in MG0003 and Pool S2.

In MG0003 and Pool S2, there were no clear trends in the incidences of TEAE categories by eGFR subgroup (Table 94); although interpretation is limited by the low number of participants in the 30-59mL/min/1.73m2.

Table 94: MG0003 (SS) and Pool S2: Overview of TEAEs by eGFR subgroup

Category	MG0003						Pool S2		
	Placebo N=67 n (%) [#]			RLZ Total N=133[a] n (%) [#]			RLZ Total N=188[a] n (%) [#] {100ER}		
	mL/min/1.73m^2			mL/min/1.73m^2			mL/min/1.73m^2		
	≥90	60–89	30–59	≥90	60–89	30–59	≥90	60–89	30–59
	n=42	n=22	n=3	n=89	n=37	n=6	n=122 Sum of Cycles=468	n=57 Sum of Cycles=188	n=8 Sum of Cycles=19
Any TEAEs	25 (59.5) [125]	17 (77.3) [49]	3 (100.0) [17]	72 (80.9) [342]	32 (86.5) [110]	5 (83.3) [22]	111 (91.0) [1063] {227.1}	49 (86.0) [397] {211.2}	8 (100.0) [65] {342.1}
Serious TEAEs	4 (9.5) [4]	1 (4.5) [1]	1 (33.3) [1]	7 (7.9) [9]	5 (13.5) [6]	0	24 (19.7) [30] {6.4}	16 (28.1) [23] {12.2}	2 (25.0) [3] {15.8}
Participant discontinuation from study due to TEAEs	2 (4.8) [2]	0	0	4 (4.5) [5]	3 (8.1) [3]	0	18 (14.8) [20] {4.3}	10 (17.5) [12] {6.4}	1 (12.5) [1] {5.3}
Permanent discontinuation of IMP due to TEAEs	2 (4.8) [2]	0	0	4 (4.5) [5]	2 (5.4) [4]	0	17 (13.9) [19] {4.1}	9 (15.8) [13] {6.9}	1 (12.5) [1] {5.3}
Temporary discontinuation of IMP due to TEAEs	1 (2.4) [1]	0	0	5 (5.6) [6]	4 (10.8) [4]	0	17 (13.9) [33] {7.1}	13 (22.8) [31] {16.5}	2 (25.0) [2] {10.5}
Treatment-related TEAEs	14 (33.3) [79]	6 (27.3) [12]	2 (66.7) [3]	52 (58.4) [178]	17 (45.9) [37]	2 (33.3) [14]	77 (63.1) [480] {102.6}	31 (54.4) [160] {85.1}	3 (37.5) [32] {168.4}
Severe TEAEs[a]	3 (7.1) [3]	0	0	12 (13.5) [13]	4 (10.8) [7]	0	34 (27.9) [43] {9.2}	15 (26.3) [32] {17.0}	1 (12.5) [1] {5.3}
Deaths (TEAEs leading to death)	0	0	0	0	0	0	2 (1.6) [2] {0.4}	1 (1.8) [1] {0.5}	0

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; CTCAE= Common Terminology Criteria for Adverse Events; eGFR=estimated glomerular filtration rate; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=number of study participants with exposure to the respective dose; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment emergent adverse event
Note: "All deaths" is based on all participants screened and refers to all deaths occurring on study.
a The RLZ totals for MG0003 and Pool S2 include 1 participant with missing eGFR.
b Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator

Geographic region

In MG0003, there were no clear trends in the incidences of TEAE categories by region (Table 95); although the majority of participants were located in Europe (N=120) or North America (N=60) and therefore interpretation is limited in the Japan (N=13) and Asia (N=7) subgroups. Although the number of Japanese and Asian study participants was low in Pool S2, no notable differences were observed in the safety profile of rozanolixizumab compared with other regions. There was a trend for a lower incidence of TEAEs across categories in the North American compared with the European subgroups (Table 95).

Table 95: MG0003 and MG0007: Overview of TEAEs by region (SS)

Category	MG0003								Pool S2			
	Placebo N=67 n (%) [#]				RLZ Total N=133 n (%) [#]				RLZ Total N=188 n (%) [#] {100ER}			
	North America N=21	EU N=41	Asia N=1	Japan N=4	North America N=39	EU N=79	Asia N=6	Japan N=9	North America N=54 Sum of Cycles= 152	EU N=114 Sum of Cycles= 443	Asia N=7 Sum of Cycles= 16	Japan N=13 Sum of Cycles= 67
Any TEAEs	14 (66.7) [36]	29 (70.7) [138]	0	2 (50.0) [17]	32 (82.1) [166]	63 (79.7) [268]	5 (83.3) [13]	9 (100.0) [27]	45 (83.3) [351] {230.9}	105 (92.1) [981] {221.4}	6 (85.7) [28] {175.0}	13 (100.0) [166] {247.8}
Serious TEAEs	2 (9.5) [2]	4 (9.8) [4]	0	0	4 (10.3) [5]	8 (10.1) [10]	0	0	10 (18.5) [11] {7.2}	30 (26.3) [43] {9.7}	0	2 (15.4) [2] {3.0}
Participant discontinuation from study due to TEAEs	1 (4.8) [1]	1 (2.4) [1]	0	0	0	5 (6.3) [5]	1 (16.7) [1]	1 (11.1) [2]	5 (9.3) [5] {3.3}	21 (18.4) [24] {5.4}	1 (14.3) [1] {6.3}	2 (15.4) [3] {4.5}
Permanent discontinuation of IMP due to TEAEs	1 (4.8) [1]	1 (2.4) [1]	0	0	0	4 (5.1) [6]	1 (16.7) [1]	1 (11.1) [2]	4 (7.4) [4] {2.6}	20 (17.5) [25] {5.6}	1 (14.3) [1] {6.3}	2 (15.4) [3] {4.5}
Temporary discontinuation of IMP due to TEAEs	1 (4.8) [1]	0	0	0	2 (5.1) [2]	7 (8.9) [8]	0	0	7 (13.0) [14] {9.2}	22 (19.3) [31] {7.0}	0	3 (23.1) [21] {31.3}
Treatment-related TEAEs	6 (28.6) [9]	15 (36.6) [73]	0	1 (25.0) [12]	16 (41.0) [57]	46 (58.2) [153]	4 (66.7) [10]	5 (55.6) [9]	25 (46.3) [105] {69.1}	71 (62.3) [462] {104.3}	5 (71.4) [18] {112.5}	10 (76.9) [87] {129.9}
Severe TEAEs[a]	1 (4.8) [1]	2 (4.9) [2]	0	0	4 (10.3) [5]	10 (12.7) [13]	2 (33.3) [2]	0	9 (16.7) [10] {6.6}	36 (31.6) [61] {13.8}	3 (42.9) [3] {18.8}	2 (15.4) [2] {3.0}
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	2 (3.7) [2] {1.3}	1 (0.9) [1] {0.2}	0	0

[#]=number of individual occurrences of the TEAE in that category; 100ER=number of TEAEs occurring in the respective cycle treatment group divided by the sum of cycles from all study participants in the respective cycle treatment group and multiplied by 100; CTCAE=Common Terminology Criteria for Adverse Events; EU=Europe; IMP=investigational medicinal product; n=number of study participants reporting at least 1 TEAE in that category; N=total number of study participants in treatment group; RLZ=rozanolixizumab; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: "All deaths" is based on all participants screened and refers to all deaths occurring on study.
Note: Asia excludes Japan.
a Severe TEAE are those with CTCAE Grade 3 or above, or those with intensity as "severe" by the investigator

2.6.8.7. Immunological events

Pool S3

In total, 2 of 162 (1.2%) study participants had pre-existing ADA before their first dose of rozanolixizumab (in either MG0003 or MG0007), and 1 of these 2 (50.0%) study participants had pre-existing Nab.

A summary of the study participant ADA and NAb status from pre-treatment Baseline up to Day 43 (1 week after the last planned dose) and Day 99 (end of the 8-week Observation Period) of each Cycle is provided in Table 96.

Table 96: Overview of ADA category by timepoint of interest and cycle (Pool S3).

Timepoint ADA category	Cycle 1 N=168 n/Nsub (%)	Cycle 2 N=98 n/Nsub (%)	Cycle 3 N=73 n/Nsub (%)	Cycle 4 N=56 n/Nsub (%)	Cycle 5 N=37 n/Nsub (%)
Pretreatment Baseline to Day 43					
ADA-NEG	112/155 (72.3)	50/90 (55.6)	31/63 (49.2)	14/36 (38.9)	7/20 (35.0)
Inconclusive	0/155	0/90	0/63	0/36	0/20
TE-POS	42/155 (27.1)	40/90 (44.4)	32/63 (50.8)	22/36 (61.1)	13/20 (65.0)
Non-TE-POS	1/155 (0.6)	0/90	0/63	0/36	0/20
TE-POS, NAb-POS	16/155 (10.3)	24/90 (26.7)	23/63 (36.5)	17/36 (47.2)	10/20 (50.0)
TE-POS, NAb-NEG	26/155 (16.8)	16/90 (17.8)	9/63 (14.3)	5/36 (13.9)	3/20 (15.0)
Non-TE-POS, NAb-POS	0/155	0/90	0/63	0/36	0/20
Non-TE-POS, NAb-NEG	1/155 (0.6)	0/90	0/63	0/36	0/20
Pretreatment Baseline to Day 99					
ADA-NEG	100/155 (64.5)	49/90 (54.4)	-	-	-
Inconclusive	0/155	0/90	-	-	-
TE-POS	54/155 (34.8)	41/90 (45.6)	-	-	-
Non-TE-POS	1/155 (0.6)	0/90	-	-	-
TE-POS, NAb-POS	30/155 (19.4)	25/90 (27.8)	-	-	-
TE-POS, NAb-NEG	24/155 (15.5)	16/90 (17.8)	-	-	-
Non-TE-POS, NAb-POS	0/155	0/90	-	-	-
Non-TE-POS, NAb-NEG	1/155 (0.6)	0/90	-	-	-

ADA=antidrug antibodies; n=number of study participants; N=number of study participants in each cycle; Nab=neutralizing antibodies; NEG=negative; Nsub=total number of evaluable participants with an ADA category defined during the corresponding analysis period; POS=positive; RLZ=rozanolixizumab; TE=Treatment-emergent.
NOTE: Baseline is defined as the last measurement before receiving the very first RLZ dose. Percentages are based on Nsub.

Effect of ADA response on clinical safety

No impact on the clinical safety of rozanolixizumab was observed in study participants who tested positive for ADA.

An overview of TEAEs up to the individual last visit with an ADA measurement for the entire population is presented by ADA category in Table 97. The incidences of TEAEs were lower or comparable in TE-POS study participants compared with ADA-NEG study participants.

Table 97: Overview of TEAS by ADA category (Pool S3)

	RLZ total (≈7mg/kg, ≈10mg/kg) (N=168) n (%) [#]			
TEAE category	ADA-NEG Nsub=81	TE-POS Nsub=73	Non-TE-POS Nsub=1	Inconclusive Nsub=0
Any TEAE	69 (85.2) [461]	63 (86.3) [491]	1 (100) [3]	0
Serious TEAEs	8 (9.9) [8]	8 (11.0) [10]	1 (100) [1]	0
Participant discontinuation from study due to TEAEs	7 (8.6) [8]	2 (2.7) [2]	0	0
Permanent discontinuation of IMP due to TEAEs	7 (8.6) [10]	1 (1.4) [1]	0	0
Temporary discontinuation of IMP due to TEAEs	11 (13.6) [20]	10 (13.7) [14]	0	0
Severe TEAEs	11 (13.6) [13]	8 (11.0) [11]	1 (100) [1]	0
TEAEs leading to death	0	0	0	0

≈=approximate dose; [#]=number of individual occurrences of the TEAE within the category; ADA=antidrug antibodies; IMP=investigational medicinal product; n=number of the study participants within the ADA category over the analysis period reporting ≥1 TEAE; N=total number of study participants; NEG=negative; Nsub=number of the study participants within the ADA category over the analysis period; POS=positive; RLZ=rozanolixizumab; TE=treatment-emergent; TEAE=treatment-emergent adverse

Note: The analysis period is from pretreatment Baseline to the individual last visit with an ADA measurement for the entire population. Baseline is defined as last measurement before receiving the very first RLZ dose. Note: (%)=n/Nsub.

Immunogenicity-related AEs may include hypersensitivity reactions, anaphylactic reactions, and injection site reactions. The incidences of TEAEs that met criteria for hypersensitivity reactions (MedDRA SMQ hypersensitivity [narrow search]) and for injection site reactions (MedDRA high-level terms [HLTs]: injection site reactions, infusion site reactions, and administration site reactions not elsewhere classified) were comparable between TE-POS and ADA-NEG study participants (Table 98). There were no anaphylactic reactions reported.

Table 98: Incidence of hypersensitivity reactions and injection site reactions by ADA Category (Pool S3)

	RLZ total (≈7mg/kg, ≈10mg/kg) (N=168) n (%) [#]			
TEAE category	ADA-NEG Nsub=81	TE-POS Nsub=73	Non-TE-POS Nsub=1	Inconclusive Nsub=0
Any hypersensitivity reactions (SMQ hypersensitivity [narrow search])	10 (12.3) [10]	10 (13.7) [14]	0	0
Any injection site reactions	11 (13.6) [15]	9 (12.3) [14]	0	0

≈=approximate dose; [#]=number of individual occurrences of the TEAE within the category; ADA=antidrug antibodies; AEOF=adverse event of focus; n=number of the study participants within the ADA category over the analysis period reporting ≥1 TEAE; N=total number of study participants; NEG=negative; Nsub=number of the study participants within the ADA category over the analysis period; POS=positive; RLZ=rozanolixizumab; SMQ=Standardised MedDRA Query; TE=treatment-emergent; TEAE=treatment-emergent adverse event Hypersensitivity reactions and injection site reactions are considered AEOFs with RLZ. Note: The analysis period is from pretreatment Baseline to the individual last visit with an ADA measurement for the entire population. Baseline is defined as last measurement before receiving the very first RLZ dose.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No specific DDI study with rozanolixizumab has been conducted.

The serum concentration of IgG-based drugs (e.g, mAbs and IVIg) and Fc–peptide fusion proteins are expected to be decreased if administered concomitantly. Two weeks after a rozanolixizumab infusion, a clinically relevant effect of rozanolixizumab on the PK or efficacy of these drugs is unlikely to occur. It is recommended to initiate these drugs 2 weeks after a rozanolixizumab infusion and monitor for attenuated efficacy of these medications when administered concomitantly with rozanolixizumab. Rozanolixizumab has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn and is not expected to have a clinically relevant effect on the disposition of highly-protein bound drugs. In the gMG Phase 3 studies, minimal reductions in albumin were observed during rozanolixizumab treatment which were not clinically meaningful.

As rozanolixizumab does not appear to affect cytokine levels in gMG patients, it is anticipated that the expression of CYP450 and consequently metabolism of CYP450 substrates is not affected by concomitant rozanolixizumab treatment.

Vaccination during rozanolixizumab treatment has not been studied and the response to any vaccine is unknown. Because rozanolixizumab causes a reduction in IgG levels, vaccination with live-attenuated or live vaccines is not recommended during treatment with rozanolixizumab.

Rozanolixizumab is a mAb and is not expected to undergo hepatic metabolism or transporter mediated disposition due to its large molecular size and lack of access to intracellular enzymes such as CYP450. Drug-drug interactions through inhibition or induction of metabolizing enzymes or transporter systems are thus not anticipated.

In the PopPK-PD analysis, the maximum IgG reduction was predicted to be higher in MG patients on Baseline steroids compared to MG patients not on steroids (77.6% vs 73.0%); this difference is not expected to be clinically relevant. Baseline steroid usage was not found to affect MG-ADL response.

Human Ig treatment may interfere with the endosomal FcRn recycling mechanism of monoclonal antibodies and thereby decrease serum concentrations of rozanolixizumab.

2.6.8.9. Discontinuation due to adverse events

Placebo-controlled study (MG0003)

Permanent discontinuation from study or IMP

The incidence of TEAEs leading to permanent discontinuation from the study, or permanent discontinuation of IMP was low. The TEAEs leading to permanent study discontinuation occurred in 2 (3.1%) study participants in the rozanolixizumab ≈7mg/kg group (arthralgia, headache), 5 (7.2%) participants in the ≈10mg/kg group with 6 TEAEs (diarrhoea, upper abdominal pain, vomiting, device [tracheal prosthesis] dislocation, pruritus and metastatic squamous cell carcinoma) and 2 (3.0%) participants in the placebo group (myasthenia gravis and myasthenia gravis crisis).

The TEAEs leading to permanent study discontinuation include those TEAEs that led to permanent withdrawal from IMP.

Temporary withdrawal of IMP

Treatment-emergent AEs that led to temporary withdrawal from IMP occurred in 3 (4.7%) study participants in the rozanolixizumab ≈7mg/kg group, 6 (8.7%) in the ≈10mg/kg group with 7 TEAEs and 1 (1.5%) in the placebo group. For the rozanolixizumab ≈7mg/kg and ≈10mg/kg treatment groups, TEAEs leading to temporary withdrawal of IMP were most frequently reported in the SOC Infections and infestations (2 [3.1%] and 4 [5.8%] study participants, respectively).

By PT, no TEAE leading to temporary discontinuation of IMP were reported by >1 study participant in any treatment group.

Pool S2

Permanent discontinuation from study or IMP

In Pool S2, TEAEs that led to permanent discontinuation from the study occurred in 29 (15.4%) study participants, including 8 (6.0%) and 21 (16.0%) participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. Differences between dose groups were driven by a higher incidence of TEAEs in the ≈10mg/kg dose group for the SOCs of Investigations and Infections and infestations (both 5 [3.8%] participants) compared with the ≈7mg/kg dose group (0% and 1 [0.8%] and respectively), and with single incidence TEAEs across various PTs leading to permanent discontinuation also occurring more frequently at the higher dose. The incidence of TEAEs leading to study discontinuation was highest in the SOC Nervous system disorders (8 [4.3%] participants), and within this SOC, the most frequently reported TEAEs were myasthenia gravis (5 [2.7%]) and myasthenia gravis crisis (2 [1.1%]). Participants with TEAEs related to MG worsening received rescue therapy and therefore met protocol-mandated withdrawal criteria.

The incidence of TEAEs leading to permanent discontinuation from the study remained low throughout repeated cyclic treatment, occurring in <7% of participants per Treatment Cycle in Pool S2.

Temporary withdrawal of IMP

Treatment-emergent AEs leading to temporary withdrawal of IMP occurred in 32 (17.0%) participants in Pool S2 (N=188), including 16 (12.0%) and 20 (15.3%) participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. The TEAEs leading to temporary withdrawal primarily occurred in the SOCs Infections and infestations (16 [8.5%] participants) and Investigations (12 [6.4%]). Overall,

the most common TEAEs leading to temporary withdrawal were blood IgG decreased in 10 (5.3%) participants and COVID-19 in 8 (4.3%) participants, which is reflective of temporary withdrawal criteria related to decreased IgG levels and COVID-19 specified in the protocols.

The incidence of TEAEs leading to temporary withdrawal of IMP showed no clear trends by Cycle.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Safety data

The clinical safety database is based on a Phase 3, randomised, double-blind, placebo-controlled study MG0003, an ongoing Phase 3 randomised OLE study MG0007 and a completed OLE study MG0004. Further, the safety of rozanolixizumab has been investigated in two phase 1 studies (UP0018 and UP0060), four phase 2 studies; one in gMG (MG0002), one in immune thrombocytopenia (ITP) (TP0001) and two in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (CIDP01 and CIDP04) and three Phase 3 ITP studies (TP0003, TP0006, and TP0004).

In study MG0003, MG0004 and MG0007, rozanolixizumab was administered at doses ≈7mg/kg or ≈10mg/kg based on a weight-tiered approach with 5 different fixed doses (280, 420, 560, 840 and 1120 mg) across 4 body weight tiers (≥35 to <50 kg, ≥50 to <70 kg, ≥70 to <100 kg and ≥100 kg). Initially, in the posology section in the SmPC 4.2, two doses were recommended in 2 body weight tiers (420 mg in ≥ 35 to < 50 kg and 560 mg in ≥ 50 kg). The applicant has updated the SmPC and proposed using the ≈7mg/kg dosing regimen that were used in the three studies, which is endorsed from a safety point of view.

Data from MG0003, MG0004, and MG0007 has been pooled in three safety pools:

- Pool S1: includes participants who received their first rozanolixizumab exposure in MG0003, MG0004 (first 6 infusions) or MG0007.

- Pool S2: is a subset of Pool S1 and consists of all rozanolixizumab-treated study participants who have undergone at least 1 Treatment Cycle (defined as at least 1 dose of rozanolixizumab in any 6-week Treatment Period) and the Treatment Cycle has been followed by an 8-week Follow-up Period. This pool excludes data from MG0004 due to the missing follow-up period.

- Pool S3: consists of data from cyclic treatment uninterrupted by chronic weekly treatment. This pool excludes data generated in MG0004 (under a chronic weekly treatment regimen), and any data generated in MG0007 (under a cyclic treatment regimen) from study participants that had previously received rozanolixizumab under a chronic weekly treatment regimen in MG0004.

In the following assessment the placebo-controlled study MG0003, Pool S1 and Pool S2 will be used as the main clinical safety database. Pool S1 will be used for exposure, Pool S2 will be used as the primary safety pool and Pool S3 will be used for immunogenicity assessment. The phase 1 and 2 studies as well as phase 3 studies in other indications will be used as supportive safety data and will be included where considered appropriate.

Study MG0003: In total 133 study participants received at least 1 dose rozanolixizumab. 64 study participants received rozanolixizumab ≈7mg/kg and 69 received rozanolixizumab ≈10mg/kg. The mean (SD) number of infusions received was 5.6 (1.0%). A total of 52 (81.3%) study participants in the rozanolixizumab ≈7mg/kg group, 48 (69.6%) in the ≈10mg/kg group, and 56 (83.6%) in the placebo group received all 6 infusions.

Pool S1: 196 study participants received at least one dose rozanolixizumab. In total 152 study participants have undergone at least 6 months of study duration, and 109 study participants at least 1-year study duration. The mean (SD) number of initiated Cycles was 3.8 (2.3).

Pool S2: 97 participants have undergone at least 1 year of participation in MG0003 and MG0007. Study duration of >1/2 year was achieved by 148 participants.

Overall, the safety database consisting of a total of 152 patients treated and observed with rozanolixizumab for at least 6 months and a total of 109 patients treated and observed with rozanolixizumab for at least 12 months is, despite the low prevalence of the disease (approximately 15-20 per 100.000), considered small and hardly fulfils the recommendations according to the current Guideline ("*To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually, 300-600 patients should be adequate*." and "*100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base*" source: Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95)). Indeed, rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the few patients included. The applicant has clarified that final data from the ongoing OLE study MG0007 will be available in August 2024. In the submitted interim MG0007 CSR (data cut-off: 08 Jul 2022), a total of 47 and 0 participants reached >1 year and >2 years of time in the study, respectively. With the additional >15 months duration until the completion of the MG0007 study, it is estimated that a total of 99 and 61 participants are estimated to reach >1 years and >2 years of time in the MG0007 study. The clinical safety data from the MG0007 study will be further complemented by the proposed PASS study. Further, the applicant stated that study participants rolling over from MG0003 were re-randomised into either MG0007 or MG0004. In both OLE studies dose adjustments (to either ≈7mg/kg or ≈10mg/kg) were permitted either at the beginning of each Treatment Period (MG0007) or at any time (MG0004). As a result of this switching between doses, study participants (and their characteristic data) were allocated to the treatment group of the first Cycle, where the treatment group was determined using the maximum dose rule. This switching between doses might hamper the assessment of any dose dependency of safety parameters. The applicant explained that TEAEs were allocated to the treatment group in which the TEAE occurred either using the maximum dose rule (for by Cycle analyses) or by most recent dose. This approach seems to be prudent enough to detect an eventual imbalance of TEAE frequency and (or event rate between the two dosage groups).

Adverse events

Study MG0003: The incidence of TEAEs was similar in the rozanolixizumab ≈7mg/kg and ≈10mg/kg groups (81.3% and 82.6%) and lower in the placebo group (67.2%). Serious TEAEs was similar across placebo and rozanolixizumab ≈7mg/kg and ≈10mg/kg treatment groups (9.0%, 7.8%, and 10.1%, respectively). Severe TEAEs were more frequent in rozanolixizumab ≈10mg/kg (18.8%) than rozanolixizumab ≈7mg/kg (4.7%) and placebo (4.5%). Participant discontinuations due to TEAEs were also reported more frequent in rozanolixizumab ≈10mg/kg (7.2%) compared to rozanolixizumab ≈7mg/kg (3.1%) and placebo (3.0%). The same pattern was seen in permanent discontinuation of IMP due to TEAEs and temporary discontinuations. Treatment-related TEAEs was similar in the

rozanolixizumab ≈10mg/kg and rozanolixizumab ≈7mg/kg groups (56.5% and 50.0%, respectively) and lower in the placebo group (32.8%). No deaths were reported in the study.

Pool S2: TEAEs were reported more frequent in rozanolixizumab ≈10mg/kg (91.6%) compared to rozanolixizumab ≈7mg/kg (77.4%). Serious TEAEs were also reported more frequent in rozanolixizumab ≈10mg/kg (22.1%) compared to rozanolixizumab ≈7mg/kg (10.5%). Treatment related TEAEs were reported in 61.8% in the rozanolixizumab ≈10mg/kg group and 42.9% in the rozanolixizumab ≈7mg/kg group. TEAEs leading to deaths were reported in 2 (1.5%) participants in the rozanolixizumab ≈10mg/kg group and 1 (0.8%) in the rozanolixizumab ≈7mg/kg group. Overall, across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group.

The applicant has presented the safety data for the overall population in the summary of clinical safety, including AChR-Ab seropositive and AChR-Ab seronegative participants, MuSK antibody positive and MuSK antibody negative patients. Since the indication is restricted to AChR-Ab seropositive or MuSK antibody positive patients, the applicant was asked to present the overall safety data on AChR-Ab seropositive patients and MuSK antibody positive patients. Number of the TEAEs, event rate and frequency were lower in the anti-MuSK+ subgroup for the most SOCs. However, this kind of imbalance is the consequence of the low or even very low number of patients in the anti-MuSK+ subgroup.

The applicant provided the frequency and number of non-TEAE events for the Intermittent Periods of clinical studies for both dosage groups. No trends in favour of any treatment group could be found while comparing the event frequencies in a certain SOC except for Infections and infestations SOC (13.0% vs 6.8% in the ≈10mg/kg and ≈7mg/kg dose groups, respectively) and Musculoskeletal and connective tissue disorders SOC (2.3% vs 6.0% in the ≈10mg/kg and ≈7mg/kg dose groups, respectively). There are some imbalances at PT level, most likely due to the low number of events.

Common TEAEs

Study MG0003: The most frequent TEAEs were reported in the SOCs of nervous system disorders (57.8%, 47.8%, and 31.3% of study participants in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups, respectively). Headache were the most frequent PT within the SOC (45.3%, 37.7%, and 19.4% of study participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively). Myasthenia gravis were reported in 3 participants in each group (≈4.5%).

TEAEs within the SOC GI disorders were reported in 32.8%, 30.4%, and 23.9%, respectively in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups. Diarrhoea was the most frequent PT with the SOC with 25.2%, 15.9% and 13.4%, respectively followed by nausea (reported in 7.8%, 11.6% and 7.5% respectively).

TEAEs within the SOC general disorders and administration site conditions occurred in 25.0%, 39.1%, and 19.4%, respectively). Pyrexia was the most common reported PT within the SOC with 12.5%, 20.3% and 1.5%, respectively.

TEAEs within the SOC infections and infestations occurred in 15.6%, 30.4%, and 19.4%, in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups, respectively. Thus, infections are especially a concern in the rozanolixizumab ≈10mg/kg group. Nasopharyngitis were the most frequent PT within the SOC with incidences of 1.6%, 7.2% and 4.5%, respectively.

TEAEs within the SOC musculoskeletal and connective tissues disorders were reported in 23.4%, 18.8%, and 13.4%, in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups, respectively. The most frequent PT within the SOC were arthralgia with incidences of 6.3%, 7.2% and 3.0%, respectively.

Overall, the most common TEAEs were headache, diarrhoea, pyrexia, nausea, and arthralgia. The SOC Infections and infestations as well as the PT pyrexia were reported twice as often in the rozanolixizumab

≈10mg/kg group compared to the rozanolixizumab ≈7mg/kg group (30.4% vs. 15.6% and 20.3% vs. 12.5%). Further, oral herpes only occurred in the rozanolixizumab ≈10mg/kg group (4.3%).

Pool S2: Overall, the incidence of TEAEs was higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg dose group (91.6% vs 77.4% of participants). TEAEs were most frequently reported in the SOCs of Nervous system disorders (55.7% vs. 48.9% of study participants), Infections and infestations (41.2% vs. 32.3%), Gastrointestinal disorders (41.2% vs. 30.8), and General disorders and administration site conditions (42.7% vs. 29.3).

The most common TEAEs across both dose groups were headache (42.0% vs. 40.6 of study participants), diarrhoea (22.9% vs. 22.6%), pyrexia (18.3% vs. 10.5), nausea (14.5% vs. 9.8%), COVID-19 infection (11.5% vs. 8.3%), arthralgia (9.2% vs. 6.8%), and blood IgG decreased (10.7% vs. 4.5%).

As seen in study MG0003, infections and pyrexia as well as IgG decreased were reported more often in the rozanolixizumab ≈10mg/kg group compared to the rozanolixizumab ≈7mg/kg group. Oral herpes was reported in 6.1% in the rozanolixizumab ≈10mg/kg group and 0.8% in the rozanolixizumab ≈7mg/kg group.

Myasthenia gravis were reported in 8.4% and 5.3% in the rozanolixizumab ≈10mg/kg group and the rozanolixizumab ≈7mg/kg group, respectively, which is a concern for the higher dosing. Narratives for all MG worsening and MG crisis events have been presented. Two out of 22 were anti-MuSK positive and 20 out of 22 were anti-AChR positive. Eight participants were ADA positive prior to the event. All IgG levels immediately prior to, or at the onset of the event were equal, or lower than the respective cycle Baseline IgG level. All cases except for one were considered not related by the investigator. The event considered related by the investigator were mild and occurred on the day of first infusion. Sponsor assessment was not related. Overall, it is agreed with the applicant that the events were not considered related to treatment or IgG rebound or overshoot.

Fall was also reported with more than twofold frequency and with almost threefold event rate in the 10 mg/kg group than in the ≈7 mg/kg group of pool S2. There were 9 patients in Pool S2 who experienced Fall TEAE during the clinical studies. To investigate the MG status of these study participants a search for TEAEs related to MG worsening prevalent at the time of fall was conducted. Results of this search revealed that there was one study participant in the rozanolixizumab ≈10mg/kg group who reported recurrent falls while having ongoing TEAEs of muscular weakness. Other study participants experiencing TEAE of fall, did not experience TEAE(s) related to muscular weakness or worsening of MG meanwhile. Six out of nine study participants experiencing Fall AE were over 70 years of age. The majority of study participants had other comorbidities (e.g, hypertension, type 2 diabetes mellitus, musculoskeletal disorders) and were taking multiple concomitant medications (e.g, antihypertensive and central nervous system agents) which could potentially increase the risk of falling.

Severe TEAEs

Study MG0003: The incidence of severe TEAEs was higher in the rozanolixizumab ≈10mg/kg group (18.8%) than in the rozanolixizumab ≈7mg/kg (4.7%) and placebo (4.5%) groups. Severe TEAEs most frequently occurred in the SOC Nervous System Disorders (11.6% in ≈10mg/kg, 3.1% in ≈7mg/kg treatment groups and 3.0% in placebo). Within this SOC, headache was the most common severe TEAE with 8.7% in the ≈10mg/kg group and 1.6% in the ≈7mg/kg treatment group. No placebo-treated participant experienced severe headache.

The other TEAEs of severe intensity occurring in >1 study participant in the rozanolixizumab ≈10mg/kg or ≈7mg/kg treatment groups were diarrhoea (0 and 2.9% participants, respectively, vs 0 in placebo) and myasthenia gravis (1.6% and 2.9%, respectively vs. 1.5% in placebo. All other TEAEs of severe intensity occurred in no more than 1 study participant.

Pool S2: In total, 26.6% of study participants had severe TEAEs in Pool S2. Overall, the incidence was higher in the rozanolixizumab ≈10mg/kg (29.8%) than in the ≈7mg/kg dose group (9.0%).

The most frequently reported severe TEAEs in the total group were myasthenia gravis (5.9%) and headache (4.3%). For both PTs the frequency was higher in the ≈10mg/kg dosing group compared to ≈7mg/kg. Further infections, aseptic meningitis, IgG decreased, and diarrhoea were reported as severe more frequently in the ≈10mg/kg dose group compared to the ≈7mg/kg dose group.

Overall, headache, diarrhoea, infections, and myasthenia gravis are a concern in the rozanolixizumab ≈10mg/kg dose group with regard to severity.

Serious adverse events and Deaths, other significant events

Deaths

Five deaths were reported in study MG0007. All were assessed as unrelated to study treatment by investigator and sponsor.

Overall, 4 of 5 death were associated with infections. 3 out of the 4 infections were in the participants receiving rozanolixizumab 10mg/kg. Severe infections are a concern in this group and an impact of rozanolixizumab on the outcome of death cannot be excluded.

Serious Adverse Events

Study MG0003: The incidence of serious TEAEs was similar across the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg and placebo groups (7.8%, 10.1% and 9.0%, respectively). The most frequent serious TEAEs were myasthenia gravis (1.6%, 2.9%, and 1.5% of participants). Myasthenia gravis crisis were only reported in the placebo group (3.0%).

Pool S2: The incidence of serious TEAEs was higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (22.1% vs. 10.5% participants). This difference was predominantly driven by serious TEAEs of myasthenia gravis (6.1% vs. 3.0%) and myasthenia gravis crisis (3.1% vs. 0). The higher frequency of serious myasthenia gravis and myasthenia gravis crisis events in the rozanolixizumab ≈10mg/kg group is a concern. Further, aseptic meningitis and headache were reported in 1 patient each in the rozanolixizumab ≈10mg/kg group which is also a concern for this group.

The applicant has included a section regarding headache under the description of selected adverse reactions as requested. The applicant proposes to include ADRs observed with the relevant recommended ≈7mg/kg in the ADRs table. The applicant has updated section 4.8 with ADRs observed at ≈7mg/kg dose including angioedema. This will keep section 4.8 of the SmPC strictly to the recommended dose of ≈ 7mg/kg and remove any reference to ADRs occurring at the higher dose (≈10mg/kg). Information on the aseptic meningitis and infection ADRs observed at a higher dose has been included in section 4.4 of the SmPC.

Overall, 4 malignancies were reported in the pool (invasive ductal breast carcinoma, retroperitoneal neoplasm, thymoma and metastatic squamous cell carcinoma). Due to the short duration of exposure of rozanolixizumab and advanced presentation of malignancies at the time of diagnosis and other causal confounders (immunosuppressive, pre-existing malignancy and causal relationship between thymoma and MG), it is agreed with the applicant that the causal relationship between the events and rozanolixizumab is not related. Regarding mechanism of action there is no evidence for FcRn function or IgG reduction is correlated to increased malignancy risk.

Further, there was 1 serious event of SCLE in the rozanolixizumab ≈7mg/kg group which was considered to be related to rozanolixizumab by the investigator. The causality of the case is confounded by other autoimmune diseases (rheumatoid arthritis and hypothyroidism) and previous intermittent skin lesions and concomitant use of proton pump inhibitors that have the rare side effect SCLE. The applicant

proposes to monitor autoimmune disorders and discuss the topic in the periodic reports. This is supported.

Adverse events of focus

Headache

The applicant states that although headache is a common TEAE with rozanolixizumab, the pathogenesis of headache is unknown. However, in Patel 2020 it is stated: "*Unlike other organ systems, FcRn removes IgG from the central nervous system, putting it into the circulation by reverse transcytosis across the blood-brain barrier FcRn is expressed in brain microvascular endothelium and choroid plexus epithelium. Via FcRn, IgG is transported out of the perivascular space and interstitial fluid into the blood, a process that may limit central nervous system inflammation in pathological situations such as bacteremia.*"

A literature review on a possible link between FcRn, excess IgG in brain, headache and migraine was presented. Most publications on this matter points to FcRn NOT being responsible for transporting excess IgG out of the CNS. Hence, a physiological link behind rozanolixizumab and headache is still unknown.

Study MG0003: TEAEs for headache occurred in 48.4%, 39.1% and 19.4% participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. Severe events occurred more frequent in the 10mg/kg group (8.7%) comparted to the ≈7mg/kg group (1.6%). There was 1 serious TEAE of headache in 1 participant (1.4%) in the rozanolixizumab ≈10mg/kg group.

Pool S2: In total, 47.3% of study participants experienced any headache in Pool S2, with the incidence similar across the ≈7mg/kg and ≈10mg/kg dose groups (41.4% vs. 42.7%). The incidence of any headache did not increase with repeated cyclic treatment. Severe TEAEs of headache were reported in 0.8% in the rozanolixizumab ≈7mg/kg group and 5.3% in the rozanolixizumab ≈10mg/kg group and are indeed a concern for the rozanolixizumab ≈10mg/kg group.

Infections, including opportunistic infections

Study MG0003: Overall, 23.3% of rozanolixizumab-treated participants and 19.4% placebo-treated participants reported TEAEs within the infections and infestations SOC. The incidence was higher with rozanolixizumab ≈10mg/kg group (30.4%) compared rozanolixizumab ≈7mg/kg (15.6%).

The most frequently reported infections were nasopharyngitis, oral herpes, and upper respiratory tract infection. Urinary tract infection (UTI) was commonly reported, but its incidence was similar across treatment groups. Although the incidence of UTIs was low, there appeared to be an association between UTIs and comorbid DM in placebo-treated participants in MG0003, and in rozanolixizumab-treated participants in Pool S2. Most participants with UTIs were receiving concomitant immunosuppressive treatments, irrespective of comorbid DM. These observations were consistent with what has been described in the literature about the gMG general population. Of the infections occurring in the rozanolixizumab treatment groups, none were severe, serious, or led to permanent discontinuation from the study.

Pool S2: 45.2% of study participants experienced a TEAE within the SOC Infections and infestations. The frequency was higher in the ≈10mg/kg dose group (41.2%) compared to the ≈7mg/kg dose group (32.3%). Further, the frequency of severe infections was higher in the ≈10mg/kg dose group (4.6%) compared to the ≈7mg/kg dose group (0.8%). The most common infections by PT were COVID-19, upper respiratory tract infection, nasopharyngitis and oral herpes. The incidence of TEAEs did not increase with repeated cyclic treatment. However, the highest frequency was seen in cycle 5 (30.2%).

Serious TEAEs were also more frequent in the ≈10mg/kg dose group (4.6%) compared to ≈7mg/kg (1.5%). The most common serious TEAE within this SOC was COVID-19 (1.6%).

The applicant states that no events of opportunistic infections were observed. The applicant received Scientific Advice on the development of rozanolixizumab for the treatment of myasthenia gravis from the CHMP on 16/12/2021 (EMA/SA/0000060999) and 29/05/2019 (EMEA/H/SA/4099/1/2019/III), here it is stated: "*Patients should be monitored thoroughly for the development of opportunistic infections due to the unspecific mechanism of action of rozanolixizumab*." Investigators were required to report opportunistic infections to the Sponsor within 24h, regardless of the seriousness of the event. On a quarterly basis as a part of the routine cross-functional programme signal detection meetings, a study physician and a safety physician reviewed programmed outputs for AEs meeting criteria for opportunistic infections. Further, opportunistic infections will continue to be monitored in the post marketing settings and discussed in the periodic reports along with infections including serious infections.

Overall, as stated previously, infections, especially regarding severe and serious infections are of concern in the ≈10mg/kg dose group.

Aseptic meningitis (drug-induced aseptic meningitis)

An event of aseptic meningitis was assessed as related by the sponsor. Overall, there been 3 cases of aseptic meningitis in the clinical development programme, all assessed as related to study drug. 1 event in MG0007 in the ≈10mg/kg dose group and 2 events in another indication. Aseptic meningitis has been observed in relation to high dose IVIg (approximately 1%), less common when all IV mAb treatments (approximately 0.1%) are considered. Contrary to IVIg, as discussed earlier, it is not likely that rozanolixizumab induce increase in IgG levels in the CNS as CNS should follow systemic levels as these are lowered due to rozanolixizumab systemic inhibition of FcRn. Moreover, a literature review concluded that FcRn is not responsible for clearing excess IgG in the brain. Hence, a mechanism linking rozanolixizumab treatment to aseptic meningitis is not yet identified. However, a warning regarding aseptic meningitis has been added to section 4.4 in the SmPC.

Overall, aseptic meningitis is of concern in the ≈10mg/kg dose group.

Hypersensitivity reactions

The applicant states that the immunogenic potential of rozanolixizumab is expected to be low risk. This is not agreed due to not being fully humanised and high levels of ADA and Nab.

Study MG0003: TEAEs of hypersensitivity occurred in 10.9%, 5.8% and 1.5% of participant in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. All events were mild or moderate in severity (data not shown here). The most common event was rash (4.5% in the total rozanolixizumab group). 2 events of swollen tongue occurred in one participant. The Participant subsequently received preventive treatment for potential hypersensitivity. The first event occurred following the first infusion of rozanolixizumab ≈7mg/kg. The ADA status at the time of the event onset was negative. The second event occurred following the fourth infusion of rozanolixizumab ≈7mg/kg. The ADA status at the time of the event onset was positive. Angioedema is included in the ADR tabulated list in section 4.8 of the SmPC.

Pool S2: TEAEs of hypersensitivity occurred in 10.5% and 8.4% participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. Common TEAEs were rash (5.9%) and urticaria (1.6%). Hypersensitivity-related TEAEs were all mild or moderate except for severe rash in 1 participant. The participant with severe rash was subsequently diagnosed with SCLE (described previously).

Overall, the hypersensitivity reactions were mostly mild or moderate in severity throughout the clinical trials and the incidences did not increase with repeated cycles, which is reassuring.

Study MG0003: Injection site reactions occurred in 6.3%, 5.8% and 3.0% of study participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg group and placebo groups, respectively.

Pool S2: 9.8% of study participants and 9.2% experienced an injection site reaction in the ≈7mg/kg and ≈10mg/kg dose groups, respectively. The most frequent injection site reactions were injection site erythema (2.7%), injection site bruising, (2.1%) and injection site rash (2.1%). All injection site reactions were mild or moderate in intensity. The incidence of injection site reactions did not increase with repeated cyclic treatment.

Overall, the injection site reactions were mild to moderate in severity and the frequency is considered expected for a subcutaneously administrated antibody.

No anaphylactic reactions were reported in the either study MG0003 or pool S2.

The applicant has included a warning regarding hypersensitivity in the SmPC section 4.4. This is considered acceptable.

Gastrointestinal disturbances

The applicant states that the pathogenesis of gastrointestinal disturbances with rozanolixizumab is unknown. However, in Patel 2020 it is stated: *"Bidirectional transcytosis of IgG occurs within the intestine, both into and out of the circulation. FcRn mediates the transport of IgG into the lumen, and IgG or IgG-ICs are delivered back into the lamina propria, allowing delivery of these complexes to mucosal dendritic cells that regulate immune response. In line with this, FcRn is expressed at intestinal mucosal surfaces of the small and large intestine, including villous and crypt enterocytes, goblet cells, and subpopulations of enteroendocrine cells. IgA, the most important mucosal immunoglobulin, uses a different system of transcytosis."*

The applicant acknowledges that rozanolixizumab most likely inhibits FcRn function in the intestinal system thereby inhibiting not only the recycling but also transcytotic functions of FcRn and presentation of immune complexes to dendritic cells. From the assessor's point of view, this mechanism could dampen this one part of the normal immune defence system in the intestines potentially leading to higher incidence or severity of intestinal infections. Study MG0003: TEAEs for GI disturbances occurred in 31.3%, 27.5% and 19.4% of participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. The most common TEAEs in the rozanolixizumab groups compared with the placebo group were diarrhoea (20.3%), nausea (9.8%), vomiting (4.5%) and abdominal pain upper (3.8%) in the total rozanolixizumab group. Severe TEAEs were reported in 1 participant in the rozanolixizumab ≈7mg/kg group (vomiting) and in 2 participants in the ≈10mg/kg group (diarrhoea). Serious TEAEs were reported in for 2 participants in the rozanolixizumab ≈7mg/kg group (gastritis and vomiting). Discontinuations from the study due to GI disturbances occurred in 2 study participants in the rozanolixizumab ≈10mg/kg group (vomiting and abdominal pain upper in 1 participant; diarrhoea in 1 participant). Abdominal pain is not included in the SmPC section 4.8 since the incidences of abdominal pain were comparable between placebo and rozanolixizumab ≈7mg/kg and ≈10 mg/kg treatment groups and no severe events were reported. The event leading to discontinuation also reported vomiting leading to discontinuation.

Pool S2: 38.8% of study participants experienced any GI disturbance in Pool S2. The incidence was highest in the ≈10mg/kg dose group (36.6%) compared to the ≈7mg/kg dose group (28.6%). The most common TEAEs for GI disturbances were diarrhoea (28.7%), nausea (14.9%), abdominal pain (8.0%) and vomiting (6.9%) in the total rozanolixizumab group. The incidence of any GI disturbance did not increase with repeated cyclic treatment. 2 participants had a serious GI disturbance (gastritis and vomiting) and 3 participants had severe GI disturbances (vomiting in 1 participant and diarrhoea in 2 participants).

Hepatic events

Study MG0003: TEAEs for drug-related hepatic disorders were reported in 1 (1.6%) study participant in the rozanolixizumab ≈7mg/kg group, 4 (5.8%) in the ≈10mg/kg group, and 1 (1.5%) in the placebo group. The following PTs were reported: hepatic fibrosis, blood bilirubin increased, prothrombin time prolonged, transaminases increased, and non-alcoholic fatty liver disease. Blood bilirubin increased was reported in 2 (2.9%) study participants in the rozanolixizumab ≈10mg/kg group. All events were mild or moderate in intensity and there were no serious events or events that led to discontinuation from the study.

Pool S2: In total, 9 (4.8%) study participants had 13 TEAEs that met search criteria for drug-related hepatic disorders, including 2 (1.5%) participants in the ≈7mg/kg dose group (3 events) and 7 (5.3%) in the ≈10mg/kg dose group (10 events). There were no serious TEAEs and 1 severe TEAE (liver function test increased).

In total, 5 of the TEAEs in 4 participants were investigator-assessed as related to rozanolixizumab and all resolved: 2 TEAEs of blood bilirubin increased in 2 participants, 1 TEAE of transaminases increased in 1 participant and TEAEs of increased ALT and AST in 1 participant. The Investigator assessed that, these TEAEs of increased ALT and AST were considered to be related to rozanolixizumab and the concomitant medication Comirnaty. However, the events are not considered to be caused by drug-interactions due to lack of temporal association between administration of Comirnaty and rozanolixizumab, resolution of events while rozanolixizumab was still ongoing and newly started concomitant treatments.

There were no events meeting the criteria of Hy's law.

Overall, events related to hepatic disorders were more frequently reported in the ≈10mg/kg dose group compared to the ≈7mg/kg dose group. However, there was not recognised any specific pattern to the type of hepatic related TEAEs, temporal relationship to study treatment or dose-response relationship in the group of events.

Effects on the kidney

Treatment-emergent AEs meeting criteria for effects on the kidney comprised of renal impairment in 3 (4.3%) participants in the rozanolixizumab ≈10mg/kg group. No study participants had severe or serious TEAEs of renal impairment. All 3 participants had pre-existing medical conditions and/or low eGFR at the Baseline but none of them met the eGFR exclusion criteria (below 45 ml/min/1.73 m2) at screening.

Effects on lipids

A dose-related elevation in total cholesterol and LDL up to 65% was observed in a Phase 2 trial in patients with thyroid eye disease treated with the FcRn blocker IMVT-1401 (batoclimab) weekly for 12 weeks (Eyewire, 2021). No clinically relevant trends in lipid laboratory data shifts were identified with rozanolixizumab.

Laboratory findings

Haematology

Decrease in neutrophils were observed in study MG0003 in both the rozanolixizumab ≈7mg/kg and ≈10mg/kg groups and not in placebo. The highest decrease was observed in the total rozanolixizumab ≈10mg/kg. The mean values for leucocytes and neutrophils remained stable over time in study MG0007.

More shifts both toward low and high in leucocytes and high in neutrophils were observed in the ≈10mg/kg group compared to ≈7mg/kg and placebo in study MG0003.

In MG0003, a similar proportion of study participants had markedly low lymphocytes values ($<0.5x10^9$/L) in the rozanolixizumab ≈7mg/kg (6.3%), ≈10mg/kg (10.1%), and placebo (11.9%) groups. Markedly

abnormal low leukocytes (<2x10^9/L) and neutrophils (<1x10^9/L) occurred in 1 study participant in the ≈7mg/kg group and 1 study participant in the ≈10mg/kg group, respectively, and in none of the participants in the placebo group.

In pool S2, lymphocyte count decreased were reported in 8 (4.3%) participants in the ≈10mg/kg dosing group and 0 in the ≈7mg/kg group. Of the 8 participants with a TEAE of lymphocyte count decreased, 1 participant had an infection that was temporarily associated (start date lymphocyte count decreased 26 Nov 2021, start date mild COVID-19 on 22 Jan 2022).

Severe events and events leading to temporary discontinuation were only reported in the ≈10mg/kg dosing group.

Overall, lymphocyte count and neutrophil count decreased were observed more frequently in the ≈10mg/kg dosing group, which is a concern also regarding the higher frequency of infections and severe infection in this group.

In MG0003, the incidence of normal to low shifts from Baseline in platelet levels was similar in the placebo group (7.5%) compared with the rozanolixizumab ≈7mg/kg (3.1%) and ≈10mg/kg (2.9%) groups. The highest change from baseline results occurred in the ≈10mg/kg group. The same pattern was seen in MG0007.

Changes in platelets were also observed in the supportive studies, ie. in study TP0001, the most frequent severe TEAE was thrombocytopenia in 2 (3.0%) participants. Since the events of severe thrombocytopenia reported from TP0001 were considered unrelated to rozanolixizumab by the investigator and were confounded as thrombocytopenia is a symptom of the disease under study (ITP) in TP0001, it is agreed not to include thrombocytopenia in the ADR table in the SmPC.

There was not found any specific patterns in the other haematology parameters of concern.

Clinical chemistry

In study MG0003, a higher proportion of shifts from normal towards high in CRP in the ≈10mg/kg group (40.6%) compared with ≈7mg/kg (15.6%) and placebo (13.4%) groups were observed. This is in line with the higher frequencies of infections and shift towards high in leucocytes and high in neutrophils in this group. Further, CRP >10mg/L occurred more frequently in the ≈10mg/kg group (26.1%) compared to ≈7mg/kg (10.9%) and placebo (17.9%).

Markedly abnormal high values for glucose (>13.9 mmol/) occurred more frequent in the ≈10mg/kg group (7.2%) compared to ≈7mg/kg (3.1%) and placebo (4.5%). However, the applicant states that all of the 5 participants with TEMA high glucose values during MG0003 had glucose values above the normal range at Baseline or Screening and had repeated abnormal or MA high values in MG0003 and/or the OLE studies. All participants had BMI >30kg/m2 and were receiving concomitant prednisolone.

In study MG0003, 7.8% in the ≈7mg/kg, 8.7% in the ≈10mg/kg group and 0 participants in placebo had an IgG value ≤1g/L. In study MG0007, low IgG (≤1g/L) also occurred in 6.3% and 9.2% participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg treatment groups, respectively. There was no trend indicating a higher incidence of TEAE within the SOC Infections and Infestations in participants with lower IgG nadirs.

Albumin and total protein

Slight reductions in mean albumin levels were observed at all timepoints for both rozanolixizumab treatment groups in study MG0003 and also seen in MG0007. The applicant states that reductions were not clinically significant. Following maintenance therapy with rozanolixizumab during MG0004 for up to 1-year, slight albumin reductions were observed that were in line with what has been observed in MG0003 and MG0007 during cyclic treatment with rozanolixizumab. There was no gradual decline of

albumin levels over time. Participants shifting from albumin normal to low during study participation had mostly isolated occurrences of low albumin.

Overall, there is no sign that chronic treatment with rozanolixizumab would lead to a clinically relevant albumin reduction.

Urinalysis

There was not found any specific patterns in the urinalysis of concern.

Further, the applicant provided a table summarising all laboratory abnormalities (including clinical chemistry) of grade 3-4 CTCAE severity in all cycles in study MG0003 and pool S2 for a better overview.

No other concerns arose.

Vital signs and electrocardiograms

Overall, it seems like SBP and DBP, pulse rate, and temperature remained stable over time in both study MG0003 and MG0007.

In study MG0003, none of the participants had a QT interval or QTcF interval ≥500msec, or an increase from Baseline in QTcF interval of ≥60msec.

In study MG0007, there was1 shift in ECG parameters from abnormal not clinically significant at Baseline to abnormal clinically significant, which occurred in a study participant in the rozanolixizumab ≈7mg/kg group in Cycle 2. In the 1st degree AV block considered clinically significant in Cycle 2, the average PR interval was prolonged >200msec at Cycle 1 and Cycle 2 Baselines, and while the average PR interval was >200msec Day 43 of Cycle 2 (211.3msec), it was shorter than the Cycle 2 Baseline (220msec). At the EOS visit, all 6 ECG readings showed a 1st degree AV block that were considered non-clinically significant by the investigator, which is reassuring.

Overall, the data on vital signs and ECG looks reassuring.

Assessment of suicidality

No noteworthy Columbia-Suicide Severity Rating Scale suicidality findings were reported.

Safety in special populations

Safety by administered fixed dose

The applicant states that the incidence of TEAE categories with rozanolixizumab administered at fixed doses was similar to the incidence observed with the ≈7mg/kg and ≈10mg/kg in the MG0003 and MG0007 studies. This is agreed, since the fixed doses represent both of the weight-based groups (≈7mg/kg and ≈10mg/kg) for the 420 mg, 560 mg and 840 mg fixed dose. However, it is not agreed that the overall safety profile was similar in the ≈7mg/kg and ≈10mg/kg groups, since across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group.

Further, events within the SOC Infections and infestations are of concern since events were reported twice as often in the ≈10mg/kg group compared to the rozanolixizumab ≈7mg/kg group. Further, severe, serious infections, aseptic meningitis and deaths related to infections are of concern in the ≈10mg/kg dose group. Moreover, lymphocyte count, neutrophil count decreased, and pyrexia were observed more frequently in the ≈10mg/kg dosing group, which is a concern also with regard to the higher frequency of infections and severe infection in this group. The higher frequency of serious myasthenia gravis and myasthenia gravis crisis events in the rozanolixizumab ≈10mg/kg group is also a concern as well as severe headache. Overall, the applicant has changed the dosing regimen to ≈7mg/kg as requested.

Sex

Treatment-related TEAEs were higher in female compared with male participants in both rozanolixizumab-treated participants in MG0003 (59.5% vs 45.8%) and Pool S2 (63.1% vs 53.2%). Otherwise, no trends in the incidences of TEAE categories by sex subgroup were observed in study MG0003 and Pool S2.

Age

No specific safety concerns were identified in the elderly population. There were no clear trends in the incidences of TEAE categories by age subgroup except for the higher incidence of treatment-related TEAEs in the younger population MG0003 (62.0% vs. 27.3%) and Pool S2 (62.1% vs. 50.0%).

Weight and BMI

In MG0003, there were no clear trends in the incidences of TEAE categories by weight subgroup. However, caution should be taken due to small numbers in the <50kg subgroup.

In MG0007, across TEAE categories the incidence of TEAEs was higher in the 70kg to 100kg weight group. There was no overall trend for increasing incidence by weight, as an increased incidence was not observed in the highest weight group (≥100kg). Further, a tendency of a higher incidence of headache were observed in participants with a BMI of 18.5-<30kg/m2 compared to a BMI of ≥30kg/m2 both in study MG0003 and Pool S2. The tendency of a higher incidence of headache observed in participants with a BMI of 18.5-<30kg/m2 compared to a BMI of ≥30kg/m2 was primarily due to the lower incidence of headaches in the ≥30kg/m2 group for male in conjunction with a lower proportion of female participants in the higher BMI subgroup.

Race

The populations in both MG0003 and Pool S2 were predominantly in the White subgroup, therefore subgroup analysis by race is limited. Overall, there were no clear trends in the incidences of TEAE categories by race subgroup.

Renal impairment

In MG0003 and Pool S2, there were no clear trends in the incidences of TEAE categories by eGFR subgroup. However, caution should be taken due to small numbers in the 30-59mL/min/1.73m2 subgroup.

Geographic region

The majority of participants were located in Europe or North America and therefore interpretation is limited in the Japan (N=13) and Asia (N=7) subgroups. There was a trend for a lower incidence of TEAEs across categories in the North American compared with the European subgroups. After adjustment for the number of Cycles in Pool S2, there was no difference between the regions in event rates of any TEAE, suggesting the observed difference in incidence rate is driven by the number of cycles and extent of exposure.

Use in pregnancy and lactation

Data for the use of rozanolixizumab in pregnant women are limited since female study participants of childbearing potential were required to use a highly effective method of birth control and study drug was discontinued as per pre-specified withdrawal criteria if they became pregnant. In MG0004, 1 study participant gave birth to 1 full-term, healthy child following 4 weeks exposure to rozanolixizumab ≈7mg/kg dose in the first trimester of pregnancy.

The applicant was requested to add the following to 4.4 and 4.6 in the SmPC: "As rozanolixizumab is expected to reduce maternal antibody levels and is also expected to inhibit the transfer of maternal antibodies to the foetus, reduction in passive protection to the newborn is anticipated. Therefore, risks and benefits of administering live / live attenuated vaccines to infants exposed to rozanolixizumab in utero should be considered." The applicant has added the requested text in section 4.6. The applicant proposes to not include the proposed text in Section 4.4 to avoid duplication of information. This is acknowledged. However, a cross reference has been added from the information in 4.6 to section 4.4. (subsection "Vaccination").

Overdose

In the rozanolixizumab ITP development programme, single subcutaneous doses of rozanolixizumab 20mg/kg (up to 2162mg) were administered. The applicant provided data on TEAEs that were reported with doses of 20mg/kg compared to the events in MG0003 and Pool S2. Overall, there were no specific TEAEs occurring at the highest doses of rozanolixizumab compared with the lower doses. The applicant proposed to keep the text in section 4.9 unchanged. This is accepted.

Immunological events

Overall, the incidence of ADA and Nab were very high and increased with repeated cyclic treatment. Up to Day 43, the proportion of study participants who developed ADA increased from Cycle 1 (TE-POS: 27.1%) to Cycle 5 (65.0%) and the proportion of study participants that were NAb-POS increased from Cycle 1 (TE-POS, NAb-POS: 10.3%) to Cycle 5 (50.0%). Further, an increase in ADA and NAb incidence was observed up to Day 99 between Cycles 1 and 2: the proportion of study participants who developed ADA (TE-POS) increased from 34.8% in Cycle 1 to 45.6% in Cycle 2; the proportion of study participants that were NAb positive (TE-POS, NAb-POS) increased from 19.4% in Cycle 1 to 27.8% in Cycle 2.

It is reassuring that the frequency of hypersensitivity reactions and injection site reactions were similar in the ADA-NEG and TE-POS groups and no anaphylactic reactions occurred. Moreover, no sign of effect of ADA were seen on frequencies of TEAEs, serious TEAEs, deaths or discontinuations and the incidences of TEAEs by PT were overall consistent between TE-POS and ADA-NEG study participants. Three immune related TEAEs were reported in Pool S3 with ADA positive status. 2 of 3 TEAEs were related to pre-existing conditions. The third TEAE was Raynaud's phenomenon.

Within the hypersensitivity SMQ and administration/injection site reactions HLTs, no immune-related AE were identified. There was one study participant with a TEAE of rash, and later, the participant was diagnosed with SCLE. At the time of SCLE diagnosis, the participant's ADA status was negative. Overall, the effect of ADA on immune-related TEAEs and hypersensitivity looks reassuring.

The high frequencies of ADA and Nab is a concern and it is questioned if the provided safety data is adequate to show the effect of immunogenicity with long-term treatment. The long-term immunogenicity potential of rozanolixizumab will continue to be followed in the OLE study MG0007. At the timepoint of the submission, >1 year immunogenicity data was available for 14 study participants with gMG who received repeated cyclic treatment. With the additional >15 months duration until the completion of the MG0007 study, it is estimated that 76 study participants with gMG will have immunogenicity data over a period of at least 1 year. The additional long-term follow up of immunogenicity and information on the consequences of immunogenicity on safety will be provided in the final MG0007 CSR with a final report planned in Aug 2024.

Furthermore, the immunogenicity profile of rozanolixizumab will continue to be defined through the evaluation of the emergence of ADA and NAb and their clinical impact in the ongoing clinical programme, including data from other indications where rozanolixizumab is being used as a chronic regimen. For the gMG indication, these events will be closely monitored through routine pharmacovigilance activities discussed in the periodic safety update reports.

The further plan for ensuring immune data is considered acceptable.

The applicant propose to update the SmPC with immunogenicity text in 4.8 under "Description of selected adverse reactions". Since the immunogenicity data provided is not characterised as related to adverse reactions, but rather a precaution to the prescriber, it has been moved to section 4.4 of the SmPC. Further, unintended immunogenicity with identified effect (in this case: exposure) should be described in section 5.1 (pharmacodynamics) and 5.2, with appropriate cross-references. The applicant has updated accordingly.

Safety related to drug-drug interactions

No specific drug-drug interaction study with rozanolixizumab has been conducted.

The serum concentration of IgG-based drugs (e.g, mAbs and IVIg) and Fc–peptide fusion proteins are expected to be decreased if administered concomitantly. The applicant states that two weeks after a rozanolixizumab infusion, a clinically relevant effect of rozanolixizumab on the PK or efficacy of these drugs is unlikely to occur. It is recommended to initiate these drugs 2 weeks after a rozanolixizumab infusion and monitor for attenuated efficacy of these medications when administered concomitantly with rozanolixizumab. A recommendation to postpone initiation of treatment with these products and a precaution to monitor for efficacy response is reflected in the SmPC section 4.5. A warning has been added to the SmPC section 4.4 (with a reference to section 4.5) that the sequence of therapy initiation between established therapies for MG crisis and rozanolixizumab, and their potential interactions, should be considered. This is considered acceptable.

Post hoc analyses of efficacy outcome measures across participants with different types and numbers of gMG Baseline medications in MG0003. The analyses indicated that there was no impact of the types (corticosteroids, nonsteroidal immunosuppressants, parasympathomimetics, and combinations thereof) and number of gMG Baseline medication on efficacy outcome measures.

The risk of interaction with vaccines is reflected in the section 4.5 of the SmPC. Information regarding potential interaction with vaccines and adequate time interval between vaccines and rozanolixizumab treatment has been included as requested in section 4.4 of the SmPC.

Discontinuation due to adverse events

Study MG0003: TEAEs leading to permanent study discontinuation occurred in 2 (3.1%) study participants in the rozanolixizumab ≈7mg/kg group (arthralgia, headache), 5 (7.2%) participants in the ≈10mg/kg group with 6 TEAEs (diarrhoea, upper abdominal pain, vomiting, device [tracheal prosthesis] dislocation, pruritus and metastatic squamous cell carcinoma) and 2 (3.0%) participants in the placebo group (myasthenia gravis and myasthenia gravis crisis).

Treatment-emergent AEs that led to temporary withdrawal from IMP occurred in 3 (4.7%) study participants in the rozanolixizumab ≈7mg/kg group, 6 (8.7%) in the ≈10mg/kg group with 7 TEAEs and 1 (1.5%) in the placebo group. For the rozanolixizumab ≈7mg/kg and ≈10mg/kg treatment groups, TEAEs leading to temporary withdrawal of IMP were most frequently reported in the SOC Infections and infestations (3.1% and 5.8% study participants, respectively).

Pool S2: TEAEs that led to permanent discontinuation from the study occurred in 6.0% and 16.0% participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. Differences between dose groups were driven by a higher incidence of TEAEs in the ≈10mg/kg dose group for the SOCs of Investigations (3.8%) and Infections and infestations (3.8%) compared with the ≈7mg/kg dose group (0% and 0.8% respectively). The incidence of TEAEs leading to study discontinuation was highest in the SOC Nervous system disorders (4.3%), and within this SOC, the most frequently reported TEAEs were myasthenia gravis (2.7%) and myasthenia gravis crisis (1.1%).

TEAEs leading to temporary withdrawal of IMP occurred in 12.0% and 15.3% of participants in the rozanolixizumab ≈7mg/kg and ≈10mg/kg dose groups, respectively. The TEAEs leading to temporary withdrawal primarily occurred in the SOCs Infections and infestations (8.5%) and Investigations (6.4%). Overall, the most common TEAEs leading to temporary withdrawal were blood IgG decreased in 10 (5.3%) participants and COVID-19 in 8 (4.3%) participants, which is reflective of temporary withdrawal criteria related to decreased IgG levels and COVID-19 specified in the protocols.

In the ≈10mg/kg dosing group 2 cases of Interferon gamma release assay positive were reported in relation to discontinuations. In Pools S1 and S2, 6 participants receiving rozanolixizumab had interferon gamma release assay positive test result. The applicant provided the narratives. All events were considered not related by the investigator and sponsor. None of the participants with positive IGRA has TB-related symptoms or positive x-ray signs.

Overall, no clear signs of active or latent TB were related to the positive IGRA test and no indication that the positive test were related to rozanolixizumab treatment.

Discontinuations are primally a concern in the ≈10mg/kg group.

2.6.10. Conclusions on the clinical safety

Overall, the main safety database consisted of 196 study participants who received at least one dose rozanolixizumab. In total 152 study participants were treated and observed for at least 6 months, and 109 study participants were treated and observed for at least one year. There is no data on safety beyond two years. As rozanolixizumab is intended to be used as a chronic therapy long-term safety is included in the RMP as missing information. Indeed, rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the few patients included.

Overall, across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group. Especially serious infections are of concern in the ≈10mg/kg dose group. Therefore, the applicant has changed the dosing regimen to ≈7mg/kg as requested.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 99: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Aseptic meningitis (Drug-induced aseptic meningitis)
Important potential risks	Serious infections
Missing information	Use during pregnancy Long-term safety

2.7.2. Pharmacovigilance plan

Table 100: Summary of ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Real-world observational secondary data study (MG0027) Planned	To evaluate any potential increase in the risk of safety outcomes of interest in rozanolixizumab exposed gMG patients compared to gMG patients not exposed to rozanolixizumab.	Important identified risks: Aseptic meningitis (DIAM). Important potential risks: Serious infections. Missing information: Use during pregnancy, and Long-term safety.	Protocol submission	6 months after MA in EU
			Interim report submissions	31 Jan 2027 (progress report) 31 Jan 2029 31 Jan 2032
			Final report submission	31 Dec 2034
MG0007 Ongoing	To evaluate the long-term safety, tolerability, and efficacy of repeated 6-week treatment cycles of rozanolixizumab based on MG worsening in study participants with gMG.	Important identified risks: Aseptic meningitis (DIAM). Important potential risks: Serious infections. Missing information: Long-term safety.	Submission of clinical study report	31 Aug 2024

DIAM=drug-induced aseptic meningitis; gMG=generalised myasthenia gravis; MA=marketing authorisation; MG=myasthenia gravis.

2.7.3. Risk minimisation measures

Table 101: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Aseptic meningitis (DIAM)	**Routine risk minimisation measures:** SmPC Section 4.2 (Posology and method of administration): Treatment should be initiated and supervised by specialist healthcare professionals experienced in the management of patients with neuromuscular or neuro-inflammatory disorders. SmPC Section 4.4 (Special warnings and precautions for use). Further information is also provided in the PL (Section 2).	**Routine PhV activities beyond adverse reactions reporting and signal detection:** A specific adverse reaction follow-up questionnaire for (aseptic) meningitis will be utilised in the postmarketing setting. **Additional PhV activities:** Real-world rozanolixizumab safety study using secondary data (PASS MG0027). MG0007.
Important potential risks		
Serious infections	**Routine risk minimisation measures:** SmPC Section 4.2 (Posology and method of administration): Treatment should be initiated and supervised by specialist healthcare professionals experienced in the	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	management of patients with neuromuscular or neuro-inflammatory disorders. SmPC Section 4.4 (Special warnings and precautions for use). Further information is also provided in the PL (Section 2). **Additional risk minimisation measures:** None.	**Additional PhV activities:** Real-world rozanolixizumab safety study using secondary data (PASS MG0027). MG0007.
Missing information		
Use during pregnancy	**Routine risk minimisation measures:** SmPC Section 4.2 (Posology and method of administration): Treatment should be initiated and supervised by specialist healthcare professionals experienced in the management of patients with neuromuscular or neuro-inflammatory disorders. SmPC Section 4.6 (Fertility, pregnancy, and lactation). PL Section 2 (What you need to know before you use Rystiggo). **Additional risk minimisation measures:** None.	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None. **Additional PhV activities:** Real-world rozanolixizumab safety study using secondary data (PASS MG0027).
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.2 (Posology and method of administration): Treatment should be initiated and supervised by specialist healthcare professionals experienced in the management of patients with neuromuscular or neuro-inflammatory disorders. **Additional risk minimisation measures:** None.	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None. **Additional PhV activities:** Real-world rozanolixizumab safety study using secondary data (PASS MG0027). MG0007.

DIAM=drug-induced aseptic meningitis; NA=not applicable; PASS=post-authorisation safety study; PhV=pharmacovigilance; PL=package leaflet; SmPC=summary of product characteristics

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle

with the international birth date (IBD). The IBD is 26.06.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rystiggo (rozanolixizumab) is included in the additional monitoring list as it contains a new active substance authorised in the EU after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Rozanolixizumab is being developed as an inhibitor of the FcRn activity with the aim to reduce the concentration of (pathogenic) IgG in patients with IgG autoantibody-mediated diseases.

MG is considered a model antibody-mediated autoimmune disease, since in most cases the autoantibodies and target antigens are well-characterised. MG pathogenesis, its clinical presentation and the response of patients to therapy vary depending on the pattern of autoantibodies detected. In general, treatment goals are to treat symptoms, to manage myasthenic exacerbations and to achieve minimal manifestation status.

3.1.2. Available therapies and unmet medical need

Current treatment options include acetylcholinesterase inhibitors, short-term immune therapies such as plasmapheresis or IVIG, and long-term immune therapies with immunosuppressive agents. Thymectomy is also a treatment option. mAb such as eculizumab or rituximab are used for more refractory cases. Efgartigimod IV, ravulizumab and zilucoplan were recently approved.

A considerable variation exists in the management of gMG. There is no consensus on the choice of immunosuppressive agent and widespread use of particular agents remains. With the exception of AChE inhibitors, azathioprine, the complement inhibitors such as eculizumab, ravulizumab and zilucoplan, and the FcRn antagonist efgartigimod IV which have received regulatory approval for the treatment of gMG;

other therapies are used off-label. Some therapies are associated with an increased risk of serious side effects or patient inconvenience, which may limit their use.

Patients with AChR-Ab seronegative gMG have greater limitations on approved treatment options, as AChE inhibitors are known to have reduced efficacy or cause worsening in this population and new treatments like C5 or FcRn inhibitors are approved only for AChR-Ab seropositive patients. On the other hand, some subgroups usually greatly benefit from PLEX in contrast to their reduced response to IVIG, and they have a very good response to the administration of rituximab, possibly more pronounced than the other MG subgroups.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicentre, randomised, double-blind study aimed to show efficacy of subcutaneously infused weight-tiered (≥35kg to<50kg, ≥50kg to <70kg, ≥70kg to <100kg and ≥100kg) flat dosing regimens equivalent to ≈7mg/kg (280mg, 420mg, 560mg and 840mg) and ≈10mg/kg (420mg, 560mg, 840mg and 1120mg) rozanolixizumab administered in cycles of 6 weekly infusions versus placebo in patients with gMG who had MG-ADL score ≥3 points (with ≥3 points of the score due to non-ocular symptoms) and QMG score of ≥ 11 while receiving standard gMG treatment.

In order to assess the efficacy of MG symptom-driven repeat 6-week cyclic treatment beyond the first treatment cycle with rozanolixizumab, OLE studies were presented: MG0007 data (cutoff 08 Jul 2022) and limited data from MG0004 (first 6 weeks).

3.2. Favourable effects

At Day 43 (Visit 10), the primary endpoint was statistically and clinically significant for both rozanolixizumab treatment groups for the tested doses. The differences in LS mean change from Baseline in MG-ADL score between groups (rozanolixizumab minus placebo) were -2.586 (95% CI: -4.091, -1.249; p<0.001) for ≈7mg/kg rozanolixizumab group, and -2.619 (95% CI: -3.994, -1.163; p<0.001) for ≈10mg/kg rozanolixizumab group.

The secondary endpoints were also shown to have significant difference for rozanolixizumab in comparison to placebo. Only first two secondary endpoints are considered important (statistically and clinically significant changes of validated and well-known scales) as the next ones in testing hierarchy were in their validation phase:

1. Change from Baseline to Day 43 (Visit 10) in the MG-C score: LS mean change of -3.901 (95% CI: -6.634, -1.245; p<0.001) from Baseline in favor of rozanolixizumab ≈7mg/kg doses, and -5.525 (95% CI: -8.303, -2.968; p<0.001) in favour of ≈10mg/kg doses.
2. Change from Baseline to Day 43 (Visit 10) in QMG score: LS mean change of -3.483 (95% CI: -5.614, -1.584; p<0.001) from Baseline in favor of rozanolixizumab ≈7mg/kg doses, -4.756 (95% CI: -6.821, -2.859; p<0.001) in favor of rozanolixizumab ≈10mg/kg doses.

Other scales or analysis of interest were MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10), use of rescue therapy and minimal symptom expression (an MG-ADL total score of 0 or 1) at any time up to Day 43.

All changes summarised above are considered as clinically meaningful changes and are supportive of the primary analysis for first treatment cycle. Overall, maximum improvement was observed around Day 36 and improvement from baseline observed from Day 8. Cumulatively, 7 mg/kg doses showed a slightly numerically higher and longer response than 10 mg/kg groups on the MG-ADL scale. On the QMG scale,

the duration was similar, but 10 mg/kg groups were cumulatively reaching a numerically higher benefit level.

Preliminary results from ongoing OLE study provides exploratory efficacy data up to 4 cycles and are supportive.

3.3. Uncertainties and limitations about favourable effects

Study MG0003 evaluated one cycle and further cycles are evaluated in the MG0007. Study MG0007 is ongoing and with the data included from study MG0004, 115 AChR-Ab seropositive patients (127 overall) received two consecutive symptom driven cycles, only 69 of them followed up to 4 cycles. The long-term efficacy should be investigated further.

The addition of the 10 mg/kg dose tier in the phase III pivotal trial without a valid scientific reason or previous data in gMG to support the additional dose is not understood. The doses used in the gMG Phase 3 study were fixed doses in each of the 4 tiers (≥35kg to<50kg, ≥50kg to <70kg, ≥70kg to <100kg and ≥100kg) testing a dose-span of 5.7 mg/kg – 8.4 mg/kg or 8.1 - 12.0 mg/kg.

The different dosing regimen (2 fixed doses) that was initially recommended for labelling which was different from the regimen tested in phase III programme was changed to reflect a flat dosing for 4 weight tiers based on the ≈7mg/kg equivalent. Suggestion of flat dosing equivalent to a weight-tiered dosing of ≈10mg/kg for participants weighing ≥35 to <50kg, and 50 to <70kg while suggestion of ≈7mg/kg equivalent for participants weighing 70 to <100kg was not understood. Benefits observed with higher dose groups are not significantly different from lower dose groups.

The subgroup analyses of primary endpoint demonstrated no meaningful benefit with 10 mg/kg dose in <50 kg group (n=1) (-0.009 mean difference from placebo). The 4 patients on ≈7mg/kg rozanolixizumab out of 12 patients <50kg who have chosen to stay on therapy in MG0007 study had clinically meaningful improvement in the first cycle (-3.3 points on MG-ADL) but this benefit went back to placebo levels of improvement (-1 or-1.3 points on MG-ADL) during further cyclic treatments. These data are showing that there are some selected patients <50kg benefiting from rozanolixizumab therapy but the numbers are too small to draw any conclusions. However, an extrapolation of efficacy to this subgroup was agreed due to consistent PK/PD effects with the overall study population (approximately 70% total IgG reduction in MG0003 with 280mg dose). The median maximum percentage change from Baseline was slightly lower for the 280mg dose compared with the higher doses; however, variability was high. Moreover, this was not aligned with the total serum IgG changes per dose that seemed comparable for all doses.

MuSK-Ab seropositive subgroup was small but the subgroup analysis of MG0003 reflect evidence regarding the efficacy of rozanolixizumab treatment in anti-MuSK+ subpopulation, which was maintained throughout repeated cyclic treatment. The pharmacodynamic data, showing lowering of IgG4 in line with total IgG is further supporting these clinical findings.

3.4. Unfavourable effects

In study MG0003 the incidence of TEAEs was similar in the rozanolixizumab ≈7mg/kg and ≈10mg/kg groups (81.3% and 82.6%) and lower in the placebo group (67.2%). Severe TEAEs were more frequent in rozanolixizumab ≈10mg/kg (18.8%) than rozanolixizumab ≈7mg/kg (4.7%) and placebo (4.5%). Participant discontinuations due to TEAEs were also reported more frequently in rozanolixizumab ≈10mg/kg (7.2%) compared to rozanolixizumab ≈7mg/kg (3.1%) and placebo (3.0%). The same pattern was seen in permanent discontinuation of IMP due to TEAEs and temporary discontinuations.

In Pool S2, across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group.

In study MG0003 the most frequent TEAEs were reported in the SOCs of nervous system disorders (57.8%, 47.8%, and 31.3% of study participants in the rozanolixizumab ≈7mg/kg, rozanolixizumab ≈10mg/kg, and placebo groups, respectively). Headache was the most frequent PT within the SOC (45.3%, 37.7%, and 19.4% of study participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively). Further, severe TEAEs most frequently occurred in the SOC Nervous System Disorders (11.6% in ≈10mg/kg, 3.1% in ≈7mg/kg treatment groups and 3.0% in placebo). Within this SOC, headache was the most common severe TEAE with 8.7% in the ≈10mg/kg group and 1.6% in the ≈7mg/kg treatment group.

TEAEs for GI disturbances occurred in 31.3%, 27.5% and 19.4% of participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. The most common TEAEs in the rozanolixizumab groups compared with the placebo group were diarrhoea (20.3%), nausea (9.8%), vomiting (4.5%) and abdominal pain upper (3.8%) in the total rozanolixizumab group.

Overall, 23.3% of rozanolixizumab-treated participants and 19.4% placebo-treated participants reported TEAEs within the infections and infestations SOC. This is expected due to the mechanism of action. The incidence was higher with rozanolixizumab ≈10mg/kg group (30.4%) compared rozanolixizumab ≈7mg/kg (15.6%). With repeated cyclic treatment, infections, IgG decreased, and diarrhoea were reported as severe more frequently in the ≈10mg/kg dose group compared to the ≈7mg/kg dose group.

TEAEs of hypersensitivity occurred in 10.9%, 5.8% and 1.5% of participant in the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. All events were mild or moderate in severity. Injection site reactions occurred in 6.3%, 5.8% and 3.0% of study participants in the rozanolixizumab ≈7mg/kg, ≈10mg/kg group and placebo groups, respectively.

In Pool S2 the most common TEAEs across both dose groups were headache (42.0% vs. 40.6 of study participants), diarrhoea (22.9% vs. 22.6%), pyrexia (18.3% vs. 10.5), nausea (14.5% vs. 9.8%), COVID-19 infection (11.5% vs. 8.3%), arthralgia (9.2% vs. 6.8%), and blood IgG decreased (10.7% vs. 4.5%). Myasthenia gravis were reported in 8.4% and 5.3% in the rozanolixizumab ≈10mg/kg group and the rozanolixizumab ≈7mg/kg group, respectively. The most frequently reported severe TEAEs in the total group were myasthenia gravis (5.9%) and headache (4.3%). For both PTs the frequency was higher in the ≈10mg/kg dosing group compared to ≈7mg/kg. The incidence of serious TEAEs was higher in the rozanolixizumab ≈10mg/kg than in the ≈7mg/kg dose group (22.1% vs. 10.5% participants). This difference was predominantly driven by serious TEAEs of myasthenia gravis (6.1% vs. 3.0%) and myasthenia gravis crisis (3.1% vs. 0).

An event of aseptic meningitis in MG0007 was assessed as related by the sponsor. Overall, there been 3 cases of aseptic meningitis in the clinical development programme, all assessed as related to study drug. 1 event in MG0007 in the ≈10mg/kg dose group and 2 events in another indication. Aseptic meningitis is included in the safety specification as an important identified risk.

5 deaths were reported in study MG0007. All were assessed as unrelated to study treatment by investigator and sponsor. Overall, 4 of 5 death were associated with infections. 3 out of the 4 infections were in the participants receiving rozanolixizumab 10mg/kg.

Overall, the incidence of ADA and Nab were very high and increased with repeated cyclic treatment. Up to Day 43, the proportion of study participants who developed ADA increased from Cycle 1 (TE-POS: 27.1%) to Cycle 5 (65.0%) and the proportion of study participants that were NAb-POS increased from Cycle 1 (TE-POS, NAb-POS: 10.3%) to Cycle 5 (50.0%). Further, an increase in ADA and NAb incidence was observed up to Day 99 between Cycles 1 and 2: the proportion of study participants who developed

ADA (TE-POS) increased from 34.8% in Cycle 1 to 45.6% in Cycle 2; the proportion of study participants that were NAb positive (TE-POS, NAb-POS) increased from 19.4% in Cycle 1 to 27.8% in Cycle 2.

3.5. Uncertainties and limitations about unfavourable effects

With regard to the proposed dosing, in study MG0003, MG0004 and MG0007, rozanolixizumab was administered at doses ≈7mg/kg or ≈10mg/kg based on a weight-tiered approach with 5 different fixed doses (280, 420, 560, 840 and 1120 mg) across 4 body weight tiers (≥35 to <50 kg, ≥50 to <70 kg, ≥70 to <100 kg and ≥100 kg). In the posology section in the SmPC 4.2, two doses are recommended in 2 body weight tiers (420 mg in ≥ 35 to < 50 kg and 560 mg in ≥ 50 kg). The applicant states that the incidence of TEAE categories with rozanolixizumab administered at fixed doses was similar to the incidence observed with the ≈7mg/kg and ≈10mg/kg in the MG0003 and MG0007 studies. This is agreed, since the fixed doses represent both of the weight-based groups (≈7mg/kg and ≈10mg/kg) for the 420 mg, 560 mg and 840 mg fixed dose. However, it is not agreed that the overall safety profile was similar in the ≈7mg/kg and ≈10mg/kg groups, since across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group. Especially, severe and serious infections, aseptic meningitis and deaths related to infections are of concern in the ≈10mg/kg dose group. The higher frequency of serious myasthenia gravis and myasthenia gravis crisis events in the rozanolixizumab ≈10mg/kg group is also a concern as well as severe headache. Therefore, the applicant has changed the dosing regimen to ≈7mg/kg as requested.

Overall, the safety database consisting of a total of 152 patients treated and observed with rozanolixizumab for at least 6 months and a total of 109 patients treated and observed with rozanolixizumab for at least 12 months is, despite the low prevalence of the disease (approximately 15-20 per 100.000), considered small and hardly fulfils the recommendations according to the current Guideline. Indeed, rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the few patients included. A PASS is planned for ensuring adequate safety data. Moreover, the high frequencies of ADA and Nab is a concern and it is questioned if the provided safety data is adequate to show the effect of immunogenicity with long-term treatment. Further, the long-term safety of sustained IgG depletion is to be addressed.

3.6. Effects Table

Effects Table for rozanolixizumab in gMG (data cut-off:08 Jul 2022).

Effect	Short Description	Unit	Rozanolixizumab ≈7mg/kg N=66	Rozanolixizumab ≈10mg/kg N=67	Control N=67	Uncertainties/ Strength of evidence	References
	Favourable Effects						
MG-ADL	Change from Baseline (CFB) to Day 43 in MG-activities of daily living (ADL) score	LS Mean (SE)	- 3.370 (0.486)	-3.403 (0.494)	-0.784 (0.488)	No effect observed <50 kg, Asian/Japanese subgroups is explained by the applicant by small numbers. 1 patient <50 kg is treated in 10 mg/kg dose tiers. 7 patients <50 kg are treated in 7 mg/kg dose tiers. There is an unexpectedly high effect (-9.558 and -6.446) observed in MuSK+ subgroup (n=21 with data)	MG0003
		Difference vs Placebo	-2.586	-2.619		P=<0.001	
	Change from Baseline to Day 43 in the MG-Composite (MG-C) score	LS Mean (SE)	-5.930 (0.916)	-7.554 (0.934)	-2.029 (0.917)		MG0003
		Difference vs Placebo	-3.901	-5.525		P=<0.001	
	Change from Baseline to Day 43 in quantitative myasthenia gravis (QMG) score	LS Mean (SE)	-5.398 (0.679)	-6.672 (0.692)	-1.915 (0.682)		MG0003
		Difference vs Placebo	-3.483	-4.756		P=<0.001	
	Unfavourable Effects						
TEAEs	Incidence	%	81.3	82.6	67.2		MG0003
Severe TEAEs	Incidence	%	4.7	18.8	4.5		MG0003

Effect	Short Description	Unit	Rozanolixizumab ≈7mg/kg N=66	Rozanolixizumab ≈10mg/kg N=67	Control N=67	Uncertainties/ Strength of evidence	References
Discontinuations due to TEAEs	Incidence	%	3.1	7.2	3.0		MG0003
SOC nervous system disorders	Incidence	%	57.8	47.8	31.3		MG0003
PT Headache	Incidence	%	45.3	37.7	19.4		MG0003
PT Headache	Incidence	%	40.6	42.0		Not placebo controlled	Pool S2
PT headache (severe)	Incidence	%	1.6	8.7	0		MG0003
PT myasthenia gravis (severe)	Incidence	%	1.6	2.9	1.5		MG0003
PT myasthenia gravis	Incidence	%	5.3	8.4		Not placebo controlled	Pool S2
SOC infections and infestations	Incidence	%	15.6	30.4	19.4		MG0003
PT Covid-19 infection	Incidence	%	8.3	11.5		Not placebo controlled	Pool S2
PT Pyrexia	Incidence	%	10.5	18.3		Not placebo controlled	Pool S2
PT Blood IgG decreased	Incidence	%	4.5	10.7		Not placebo controlled	Pool S2
PT Diarrhoea	Incidence	%	22.6	22.9		Not placebo controlled	Pool S2
TEAEs of hypersensitivity	Incidence	%	10.9	5.8	1.5		MG0003
TEAEs of injection site reactions	Incidence	%	6.3	5.8	3.0		MG0003

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite recently emerging MoAs to target underlying pathology and approved new treatments, there is still an unmet medical need in gMG. This need is more evident for AChR-Ab seronegative gMG population.

Primary and important secondary endpoints are clinically and statistically significant for the pivotal MG0003 study (phase III double blinded study). However, the pivotal study only covers the first treatment cycle with rozanolixizumab and does not evaluate re-treatment driven by symptoms which would happen in real life. As this treatment is recommended as a chronic treatment (a different use than IVIG and PLEX for myasthenic crisis or impending crisis as rescue therapies) lack of blinded data beyond 1st cycle is concerning. This is partially addressed by ongoing MG0007 study up to 4 cycles in an open label design.

However, the serious issue about the dossier was the fact that due to extremely complex and ever-changing dosing regimen throughout the clinical development programme, the exact number of patients treated with the doses suggested for labelling and the precise effects or B/R observed remain unknown. The doses (280mg, 420mg, 560mg, 840mg and 1120mg) in phase III programme were testing a dose-span of 5.6 mg/kg –12.0 mg/kg. Initially, 2 fixed doses were suggested for labelling: 420mg below 50kg and 560mg above 50kg. Benefits observed with higher dose groups were not significantly different from lower dose groups. No meaningful benefit was observed in <50kg weight groups which is a very small group and there is no clinical data for patients above 100kg with the dose recommended. However, the applicant finally proposed a dosing regimen that reflects the ≈7mg/kg group which was implemented in the SmPC.

Results from the limited number of patients treated with 7 mg/kg rozanolixizumab (n=5) in MuSK-Ab seropositive subgroup suggest a benefit for these patients with a very high unmet medical need.

Overall, the safety database consisting of a total of 152 patients treated and observed with rozanolixizumab for at least 6 months and a total of 109 patients treated and observed with rozanolixizumab for at least 12 months is considered small and hardly fulfils the recommendations according to the current guideline. Indeed, rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the few patients included also considering that the changing of dosing regimen from phase 2 to phase 3 and then to the proposed dosing for the SmPC. Especially missing the impact of immunogenicity and IgG depletion over time when used as chronic treatment is concerning.

Across all TEAE categories, the incidence of TEAEs were higher in the rozanolixizumab ≈10mg/kg compared to the ≈7mg/kg group. Especially severe- and, serious infections, aseptic meningitis and deaths related to infections are especially of concern in the ≈10mg/kg dose group. The higher frequency of serious myasthenia gravis and myasthenia gravis crisis events in the rozanolixizumab ≈10mg/kg group is also a concern as well as severe headache. Therefore, the applicant has changed the dosing regimen to ≈7mg/kg.

3.7.2. Balance of benefits and risks

Overall, administered rozanolixizumab doses in comparison to placebo has demonstrated its efficacy at the end of the first treatment cycle in gMG population studied in study MG0003, as rated by patients and physicians. Safety profile for 7 mg/kg equivalent dosing is considered manageable.

Beyond the first cycle, the data is considered limited and maintenance of efficacy or safety in the long-term is currently unknown. The applicant has committed to provide the final study report from the ongoing extension study when available.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Rystiggo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rystiggo is not similar to Soliris and Vyvgart within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rystiggo is favourable in the following indication(s):

Rystiggo is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that rozanolixizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.