EU-RISK MANAGEMENT PLAN FOR

ROZANOLIXIZUMAB

140MG/ML, SOLUTION FOR INJECTION

Version 2.0

Date: 04 Nov 2024 20241104-rmp-v2.0- RTN-003895

Table of Contents

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 2.0

Data lock point for this RMP: Clinical data related to MG0007 has a data lock point of 12 Apr 2024. Post marketing has a data lock point of 25 Dec 2023 for pharmacovigilance and 30 Jun 2024 for exposure.

Date of final sign off: 04 Nov 2024

Rationale for submitting an updated RMP: The Phase 3 open-label extension study MG0007 was included in the Pharmacovigilance Plan as an additional pharmacovigilance activity with submission of the final clinical study report as milestone. The MG0007 study has since been completed.

Summary of significant changes in this RMP: Updated to v2.0 following approval by European Commission.

Other RMP version under evaluation: Not applicable.

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

Please see the electronic signature of the EEA QPPV or his deputy on the last page of this report.

LIST OF ABBREVIATIONS

AChR	acetylcholine receptor
AE	adverse event
AHR	adjusted hazard ratio
ALS	amyotrophic lateral sclerosis
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CSR	clinical study report
DIAM	drug-induced aseptic meningitis
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FcRn	neonatal Fc receptor
GI	gastrointestinal
GLP	Good Laboratory Practice
gMG	generalized myasthenia gravis
HUVEC	umbilical blood vein endothelial cells
ICD	immune complex disease
ICH	International Council for Harmonisation
Ig	immunoglobulin
iv	intravenous
IVIg	intravenous immunoglobulin
KLH	Keyhole Limpet Haemocyanin
MG	myasthenia gravis
MuSK	muscle-specific kinase
NK	natural killer
NMJ	neuromuscular junction
OLE	open label extension
PASS	post-authorization safety study
PD	pharmacodynamic
PLEX	plasma exchange
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan

sc	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics
TDAR	T-cell dependent antibody response
TEAE	treatment-emergent adverse event
TNHIRD	Taiwan National Health Insurance Research Database

PART I PRODUCT OVERVIEW

Table Part I–1: Product overview

Active substance	Rozanolixizumab
Pharmacotherapeutic group(s)	L04AG16
Marketing Authorization Applicant	UCB Pharma S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Rystiggo
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Rozanolixizumab is a recombinant, humanized anti-FcRn IgG4P monoclonal antibody.
	Summary of mode of action: Inhibition of IgG binding to FcRn, resulting in a reduction of the concentration of IgGs, including pathogenic IgG autoantibodies.
	Important information about its composition: Produced by recombinant DNA technology from a dihydrofolate reductase-deficient Chinese Hamster Ovary DG44 cell line. No other materials of animal origin are used in the manufacturing process.
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labeling and Package Leaflet
Indication(s) in the EEA	Current: Rystiggo is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive.
	Proposed: Not applicable.
Dosage in the EEA	Current: A treatment cycle consists of 1 dose per week for 6 weeks. The recommended total weekly dose of Rystiggo is 280mg for patients ≥35 to <50kg, 420mg for ≥50 to <70kg, 560mg for ≥70 to <100kg, and 840mg for ≥100kg.
	Proposed: Not applicable.
Pharmaceutical form(s) and strength(s)	Current: Solution for injection 140mg/mL Each 2mL vial contains 280mg of rozanolixizumab.
	Proposed: Not applicable.

Table Part I–1: Product overview

Is/will the product be subject to additional monitoring in the EU?	Yes

AChR= acetylcholine receptor; ATC=Anatomical Therapeutic Chemical; DNA=deoxyribonucleic acid; EEA=European Economic Area; FcRn=neonatal Fc receptor; gMG=generalized myasthenia gravis; IgG=immunoglobulin G; mAb=monoclonal antibody; MuSK=muscle-specific kinase; RMP=risk management plan

PART II SAFETY SPECIFICATION

Part II Module SI Epidemiology of the indication(s) and target population(s)

SI.1 Myasthenia Gravis

Based on clinical, epidemiological, immunological, and genetic findings and thymus pathology, myasthenia gravis (MG) can be subclassified. Pure ocular MG is distinguished from generalized MG (gMG). Generalized MG is subdivided into early onset (≤50 years) and late onset (>50 years) (Mukharesh and Kaminski, 2019). Early onset MG is often associated with lymphofollicular hyperplasia of the thymus, and late onset MG is characterized by age-dependent involution of the thymus. Approximately 10–15% of all patients have thymoma (thymoma-associated MG) (Melzer et al, 2016).

Myasthenia gravis is an organ-specific, antibody-mediated autoimmune disease. The pathogenic autoantibodies against the acetylcholine receptor (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.

Muscle-specific kinase (MuSK) is an NMJ protein that is specifically expressed at the postsynaptic membrane, where it colocalizes 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 hypothesized to prevent the assembly of functional protein complexes at the NMJ, thereby inhibiting AChR clustering (Shiraishi et al, 2005).

SI.1.1 Incidence

Published literature suggests that the incidence rate of MG (all subtypes) varies with age, gender, and ethnic groups (Meriggioli and Sanders, 2009). Estimates of incidence range from 0.3 to 2.8 per 100,000 person-years worldwide. In European countries, the annual incidence rate reported ranges from 0.4 (Norway) to 2.1 (Italy) per 100,000 person-years (Deenen et al, 2015). In a recent study using primary care data from the Clinical Practice Research Datalink (CPRD), incidence of MG in the UK between 2015 and 2019, was 2.46 per 100,000 person-years (95% confidence interval [CI] 2.34-2.59) (Carey et al, 2021).

SI.1.2 Prevalence

Published epidemiological studies indicate that the estimated prevalence of MG (all subtypes) in the EU is around 2.07 per 10,000 persons (95% CI 2.01-2.13). The prevalence estimate has been calculated, prioritizing more recent studies over studies that allow for age and sex standardization. The studies included reported prevalence for the period from 2010 until 2015 and incorporated data from Latvia (Zieda et al, 2018), Spain (Aragonès et al, 2017), Portugal (Santos et al, 2016), Slovakia (Martinka et al, 2018), and Sweden (Fang et al, 2015). The prevalence ranged from 1.12 per 10,000 persons in Portugal to 3.29 per 10,000 persons in Spain.

Prevalence estimates of MG from a recent study using primary care data from CPRD in the UK, calculated on 1 Jan 2019, was 3.37 per 10,000 (95% CI 3.27-3.47) (Carey et al, 2021).

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.

SI.1.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The incidence of MG increases with age, therefore the disease is most prevalent in those of older age (Carr et al, 2010). Most studies show MG incidence increasing for men with the peak at the 60-80 years age band, while in women MG incidence appears to have a bimodal age distribution with a peak at 20-40 years then again at 50-70 years (Carr et al, 2010; McGrogan et al, 2010).

A study using the US Nationwide Inpatient Sample found that in the US between 2000 and 2005, black women had a higher adjusted incidence rate of MG when compared to black men, white women and white men (Alshekhlee et al, 2009).

Family history of systemic lupus erythematosus (SLE) was found to be associated with an increased risk of gMG in a study using the Taiwan National Health Insurance Research Database (TNHIRD) (Kuo et al, 2015). Another study in the same database found that risk of gMG was higher in patients with allergic conjunctivitis, allergic rhinitis, Hashimoto's thyroiditis, Graves' disease, and diabetes mellitus (Yeh et al, 2015).

SI.1.4 The main existing treatment options

Existing treatment methods

Myasthenia gravis is a heterogeneous disease which is reflected by numerous disease subcategories that can be considered based on presence or absence of autoantibodies (AChR-MG, muscle-specific MuSK-MG, sero-negative-MG), weakness distribution (ocular MG, gMG), age at onset (childhood MG, early-and late-onset MG), and thymus histology (thymoma, non-thymoma), and thus no single treatment approach is suited for all patients. Recently completed clinical studies in MG differ in study design by severity of disease, treatment duration, primary endpoints, steroid tapering protocols, the principal analytic approach, and often contain too narrow of eligibility criteria, making generalization of study results difficult (Benatar et al, 2018). In the relative absence of evidence from controlled randomized clinical studies (Mantegazza et al, 2011) and no internationally accepted standard of care in MG, various MG treatment guidelines were recently published.

An "International consensus guidance for management of myasthenia gravis" (Sanders et al, 2016) was developed following appointment of a Task Force of 15 international experts by the Myasthenia Gravis Foundation of America in Oct 2013. In Feb 2019, all previous recommendations were reviewed and new consensus recommendations were developed on topics that required inclusion or updates based on the recent literature (Narayanaswami et al, 2021). The European Federation of Neurological Societies published "Guidelines for treatment of autoimmune neuromuscular transmission disorders" (Skeie et al, 2010). Also, national neurological societies have issued recently recommendations for MG treatment, eg, the Association of British Neurologists (Sussman et al, 2015) and the German Neurological Society

(Wiendl and Meisel, 2023) and Italian recommendations for the diagnosis and treatment of MG (Evoli et al, 2019).

Treatment approaches for MG can be classified into the following categories (Evoli and Damato, 2023):

- Conventional therapy:
  - Symptomatic therapy: drugs that immediately improve neuromuscular transmission: acetylcholinesterase inhibitors, eg, pyridostigmine
  - Immunosuppressive treatment
    (1) Glucocorticoids: prednisone, prednisolone
    (2) Immunosuppressants: anti-metabolites (azathioprine, mycophenolate mofetil, methotrexate), calcineurin inhibitors (cyclosporine, tacrolimus) and the alkylating agent cyclophosphamide
    (3) Short-term treatments: plasma exchange (PLEX), intravenous immunoglobulin (IVIg), subcutaneous Ig (SCIg)
    (4) Thymectomy: indicated in all patients with thymoma, onset of full efficacy can take several years
- Novel therapeutic options
  - B cell targeting agents: rituximab
  - Complement inhibitors: eculizumab, ravulizumab
  - Blocking of the FcRn: efgartigimod

- Generally, the choice of 1 or more of the immunomodulatory/immunosuppressing agents will be effective in most of the patients with MG. However, side effects of existing therapies (most of them used off-label) represent a major challenge. Careful consideration of the benefits and risks for the individual patient and the urgency of treatment defines the short-term, intermediate-term, and long-term treatment objectives. Special treatment considerations in adult patients are to be taken for the patient in “crisis”, the “refractory” patient, and for female patients and their partner in case of pregnancy or planning of pregnancy.

Recently, rozanolixizumab and zilucoplan have been approved for the treatment of gMG (Iorio, 2024) (see details in Table Part II–1).

Products approved for the treatment of MG (EU)

Table Part II–1 presents the products authorized for the treatment of MG in the EU.

Table Part II–1: Products approved for the treatment of MG (EU)

Drug name (trade name)	Marketing authorization holder	Authorized indication
Cholinergic agents		
Pyridostigmine bromide (Mestinon®)	Mylan Products Ltd	MG

Table Part II–1: Products approved for the treatment of MG (EU)

Drug name (trade name)	Marketing authorization holder	Authorized indication
Cholinergic agents		
Neostigmine bromide	Alliance Pharmaceuticals Ltd	MG
Distigmine bromide (Ubretid®)	Takeda	MG
Neostigmine methylsulfate (Prostigmine®)	Hameln Pharmaceuticals Ltd; Meda Pharma	MG
Atropine sulphate	Concordia International	In the treatment of cholinergic crisis of MG[a]
Immunomodulating treatment		
Glucocorticoids and other immunosuppressive products		
Prednisolone (Decortin® H)	Merck Serono GmbH	Certain forms of muscle paralysis (MG) (azathioprine being the first choice)
Azathioprine (Imurek®)	Aspen Pharma Trading Ltd	gMG
IVIg (Gamunex®-C)	Grifols Deutschland GmbH	Severe acute exacerbations of MG in adults
Biologics		
Eculizumab (Soliris®)	Alexion Pharmaceuticals, UK Ltd	Refractory gMG in patients who are AChR antibody-positive
Efgartigimod (Vyvgart®)	Argenx BV	Add-on to standard therapy for the treatment of adult patients with gMG in patients who are anti-AChR positive
Ravulizumab (Ultomiris®)	Alexion Pharmaceuticals, UK Ltd	Add-on to standard therapy for the treatment of adult patients with gMG in patients who are anti-AChR positive
Rozanolixizumab (Rystiggo®)	UCB Pharma S.A.	Add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK positive
Zilucoplan (Zilbrysq®)	UCB Pharma S.A.	Add-on to standard therapy for the treatment of adult patients with gMG in patients who are anti-AChR positive

AChR=anti-acetylcholine receptor; IVIg=intravenous immunoglobulin; gMG=generalized myasthenia gravis; MG=myasthenia gravis; MuSK=muscle-specific kinase

[a] Cholinergic crisis results from an overdose of acetylcholinesterase inhibitors

Products used off-label for the treatment of MG (EU)

Several immunosuppressants including biologics are used off-label for the treatment of MG; eg, rituximab (MabThera®), cyclophosphamide, ciclosporin, methotrexate, mycophenolate mofetil, and tacrolimus. In addition, PLEX is used off-label for the treatment of MG (Janzen, 2018).

SI.1.5 Natural history of the indicated condition in the MG population, including mortality and morbidity

There are 2 clinical subtypes of MG, ocular and gMG: in ocular myasthenia, the weakness is limited to the eyelids and extraocular muscles; in the generalized disease, the weakness commonly affects extraocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

The majority of the patients with MG present with diplopia and/or ptosis (approximately 85%) and 15% with bulbar symptoms, including dysarthria, dysphagia, and dyspnea. Dysphagia may cause coughing and choking during and after meals, and chewing fatigue is common. Approximately 10% of patients will present with limb or neck weakness. The hallmark symptom of MG is fluctuating and fatigable weakness that is worse at the end of the day and during or following exertion and improves with rest. Patients may develop a flaccid dysarthria that worsens with prolonged talking (Duffy, 2013). Isolated respiratory failure has been reported in 1% of patients. Myasthenia gravis symptoms are exacerbated by heat, stress, infection, a variety of drugs, and rarely vaccines (Gwathmey and Burns, 2015). Ocular symptoms are the first and sole manifestation in about 50% of patients. Of these patients, 50-80% progress to develop gMG, usually within 2 years (Gilhus et al, 2019).

During the natural course of MG it is estimated that 57% of patients experience general improvement, and remission is seen in 13% of patients after the first 2 years.

Risk factors for progression to generalized disease include adult-onset ocular MG, abnormal repetitive nerve stimulation findings, thymoma (Guo et al, 2021) and seropositivity for AChR antibody (Guo et al, 2021; Kemchoknatee et al, 2021). Several studies have reported increased MG severity in women than in men (Boscoe et al, 2019; Engel-Nitz et al. 2018), including a recent cohort study of 70 patients followed over 7 years and using objective and patient-reported outcome measures (Thomsen et al, 2021). Significant progress has been made in the last 2 decades around our understanding of the disease, leading to new treatment modalities and a significant reduction in morbidity and mortality. However, although a high proportion of patients respond well to conventional treatment, drug-free remission is rare, chronic immunosuppression is usually needed, and 10-15% of patients have refractory disease (Schneider-Gold et al, 2019). Moreover, severe weakness symptoms can be accompanied by higher mortality; 20% of patients remain unchanged, with mortality from the disease of 5–9% (Dresser et al, 2021; Grob et al, 2008).

If not adequately treated, gMG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. This can potentially lead to the most dangerous complication of gMG, known as myasthenic crisis, requiring hospitalization, intubation, and mechanical ventilation. Up to 20% of patients with gMG will experience a myasthenic crisis, 75% of them within 2 years of diagnosis (Shanker and Ramizuddin, 2014).

Mortality

A study in Denmark compared 702 patients with AChR positive MG diagnosed between 1985 and 2005, and followed up until 2009, with an age and sex matched cohort of 7,020 patients without MG, and found an overall adjusted mortality rate ratio of 1.41 (95% CI 1.24–1.60). Mortality was highest in the 5 years following onset of MG (Hansen et al, 2016).

A systematic review of 8 studies carried out between 1950 and 2007 showed a range in mortality rates due to MG of 0.06 -0.89 per million person-years (Carr et al, 2010). Cardiovascular disease and malignancy were the most common causes of death in patients with MG, as is the case in the general population (Christensen et al, 1998).

The Nationwide Inpatient Sample study carried out in the US between 2000 and 2005, estimated the in-hospital mortality rate to be 2.2% in patients with MG in general, and 4.5% for those admitted with myasthenic crisis. Independent risk factors for mortality in this population were age, diagnosis of myasthenic crisis and respiratory failure requiring intubation (Alshekhlee et al, 2009).

One US study of 1976 patients with MG found that mortality from MG decreased progressively during 1958–2000 compared to 1940–1957. The mortality rate has been consistently, but not significantly, higher in males (14%) than females (11%). The mean duration of MG at the time of death increased from 4.8 to 5.9 years during 1940–1965 to 10.3 to 8.6 years during 1966-2000. This duration did not differ significantly between males and females at any time point. The age of patients who died of MG increased significantly during 1966–2000 compared to 1940–1965 in both sexes (Grob et al, 2008).

Morbidity

Evidence of an initial MG exacerbation following corticosteroid treatment from a systematic review including 27 retrospective studies showed the highest rates with cortisone administration and the lowest rates with methylprednisolone (Lotan et al, 2021). Most exacerbations were of mild or moderate severity (31%) and only 8% severe. Risk factors for initial exacerbation were administration of high daily dose or alternate day prednisolone, older age, gMG, bulbar symptoms, MG severity, presence of thymoma and thymectomy. However, methodology and treatment (eg, frequency and dose) were highly heterogeneous across studies and there was a lack of appropriate comparators and adjustment for confounding. Treatment for MG can increase the risk of coexisting disorders. Prednisolone necessitates prophylaxis against osteoporosis, and patients should be monitored for weight gain, elevations in blood glucose levels, and hypertension. A recent single-center study in the USA, based on the medical review of charts from patients (N=39) with gMG treated with oral corticosteroids for ≥1year, reported a median number of corticosteroid-related adverse side effects of 2 per patient (Johnson et al, 2021). These side effects were more common in patients treated with >30mg/day prednisone (compared to ≤30mg/day). Pre-diabetes and weight gain were the most common. Weight gain and irritability were more prevalent in women and osteoporosis and pre-diabetes in men. Anticholinergic drugs for symptomatic treatment have transient and dose-limiting effects on the autonomic nervous system most often involving the gastrointestinal (GI) tract (eg, diarrhea, abdominal pain or cramps) as well as urinary urgency and increased sweating (Gilhus et al, 2016).

SI.1.6 Important comorbidities

There are a number of comorbidities which occur at a higher rate in patients with MG, and these represent a major challenge for patients with MG. Comorbidity may be crucial for quality of life, daily functions, short-term and long-term outcome, and even mortality (Gilhus et al, 2015). Presence of risk factors for comorbidities, MG complications and treatment side effects constitute the major mechanisms for additional health impairment in MG. Patients with generalized MG and comorbidities have a poorer prognosis than patients with MG alone (Laakso et al, 2021). The risks of the medicinal product are evaluated based on the characteristics of the medicinal product (eg, documented in clinical trials) and the context of use: expected comorbidities and co-medications in the target population. Patients with unexpected deterioration, lack of therapeutic response or new symptoms/signs should always be examined for comorbidity. Common comorbidities found in patients with MG include:

- Other autoimmune diseases: amongst patients with MG, it is estimated that approximately 15% of patients have a second autoimmune disease (Gilhus et al, 2015), which occurs most frequently in patients with early-onset MG and thymic hyperplasia. Thyroid disease is the most common coexisting condition, followed by SLE and rheumatoid arthritis. Type 1 diabetes is also common. In a study conducted in a referral center of 253 patients with MG in Mexico, abnormal thyroid function testing was found in 19% of patients with MG, 13% presented hypothyroidism and 6% hyperthyroidism (Cacho-Diaz et al, 2015). Amongst patients with dysthyroidism, 98% had gMG. Neuromyelitis optica with aquaporin-4 autoantibodies has a specific association with MG and can occur either before or after the onset of MG
- Respiratory disease: a study over several decades has reported 39% of patients with MG had reduced vital capacity, and 19% of those with severe gMG experienced an MG crisis with a need of assisted ventilation. However, mortality during MG crisis has been reduced to approximately 4%, and in well-treated MG populations there is no longer any overrepresentation of death due to respiratory disease (Gilhus et al, 2015)
- Malignancy: studies that compared the cancer risk in MG patients and controls are limited, with lymphomas and a few other cancer types being reported with slightly increased frequency (Gilhus et al, 2015). A study from Taiwan comprising 2614 MG patients reported a higher risk of extrathymic cancers with an incidence rate ratio of 1.38 (95% CI: 1.12-1.68) compared with matched controls during an average follow-up of 8 years (Liu et al, 2012). A nationwide case-control study in Denmark did not find that non-thymoma MG was associated with an increased overall risk for cancer (Pedersen et al, 2014). A nationwide Swedish cohort study showed that 22.4% of 2812 MG patients developed extrathymic cancer (Verwijst et al, 2021). In addition, patients with resected thymoma had an increased risk of developing metachronous second tumors (incidence ratio 1.94, 95% CI: 1.29-2.81) (Filosso et al, 2013). Further, immune-mediated diseases, including MG, may increase the risk for carcinogenesis in general. The UK Biobank study found that any immune-mediated disease, including MG, is related to a slight increased risk of total cancer, with a hazard ratio (HR) of 1.08 (95% CI: 1.04-1.12) (He et al, 2022).
- Heart Disease: cardiomyositis may occur more often in MG than in other autoimmune disorders. In population-based studies, patients with MG do not have more frequent heart

disease or heart disease mortality. However, autonomic function tests of the heart in patients with MG have shown instability in the sympathetic or parasympathetic systems (Gilhus et al, 2015)

- Nervous system disorder: patients with thymoma MG have an increased risk for autoimmune encephalitis. Registry-based studies report a relationship between autoimmune disease and schizophrenia. Amyotrophic lateral sclerosis (ALS) occurs in patients with MG more often than would be expected based on the risk in the general population (Gihus et al, 2016). In a registry-based study, MG was reported in 36 patients with ALS compared with an expected number of 7.2 (Gilhus et al, 2015)
- Diabetes: findings from a registry-based population study conducted in Norway showed that insulin treatment was prescribed almost three times more often in patients with MG than in the general population (Andersen et al, 2014). In a study conducted in a referral center in Mexico, diabetes mellitus was diagnosed in 20% of patients with MG (Cacho-Diaz et al, 2015)
- Dyslipidemia: in the Oxford Myasthenia Centre registry, hypercholesterolemia was amongst the most common comorbidities in MG and prevalence was higher in patients with late onset MG than in those with early onset (41.2% vs. 23.8%) (Klimiec-Moskal et al, 2021). In a referral centre in Mexico, dyspipidemia was diagnosed in 60% of patients with MG (Cacho-Diaz et al, 2015)
- Osteoporosis: this is a progressive bone disease characterized by low mineral density and microarchitectural deterioration of bone tissue that leads to an increased risk of fragility fracture. Osteoporosis is a common adverse effect of long-term oral corticosteroids, which is often used for the management of patients with MG. It is also more common in postmenopausal women, men over 50 years and individuals with rheumatoid arthritis and diabetes. A recent study based on linkage of national registries in Denmark found no increased frequency of major osteoporotic fracture in patients with MG (Safipour et al, 2021). A previous population-based study conducted in the UK had also found that the risk of any fracture and osteoporotic fracture did not differ between individuals with MG and age- and sex-matched controls irrespective of corticosteroid use (Pouwels et al, 2013). Effective prophylaxis against osteoporosis is important and might explain the reason for few fractures (Gilhus et al, 2015)
- Depression and anxiety: can occur in patients with MG, combined with a reduced health-related quality of life. A review of psychiatric comorbidity in patients with MG, reported that one-third of patients have depression, and up to 46.3% are diagnosed with an anxiety disorder (Law et al, 2020). Risk factors for depression were longer MG disease duration, disease severity and MG-induced respiratory failure. Treatments with hypnotics, sedatives and antidepressant drugs were 1.2-1.5 more common in an national MG population compared with controls in Norway (Andersen et al, 2014)
- Hypertension: in a study based on the analysis of the Oxford Myasthenia Centre registry, hypertension was the most common comorbidity in patients with MG (up to 58.4% in late onset MG) (Klimiec-Moskal et al, 2021). While the prevalence of arterial hypertension has been found to be lower in MG than in the general population, the use of corticosteroids and

the number of emergency visits in patients with hypertension was higher in patients with than without MG (Cacho-Diaz et al, 2015)

- Infection: 3 factors may increase the risk of infection in people with MG, muscle weakness, autoimmune disease mechanism and immunosuppressive treatment (Gilhus et al, 2018). First, higher risk of lower respiratory infections may result from weakness in the respiratory muscles or from aspiration pneumonia caused by dysphagia. Pelvic muscle weakness might also increase the risk of urinary tract infections. Second, thymus disorder or thymectomy could also predispose to infections or to infection severity. Third, patients with MG often receive prolonged treatment with and high doses of immunosuppressive drugs, which can also increase the risk of infection. Two longitudinal studies compared the incidence of infection between the MG and the general population. Kassardjian et al (2020), conducted a population-based cohort study in Ontario, Canada, in the period between Apr 2002 and Dec 2015 (Kassardjian et al, 2020). The study used linked health administrative data and included 3,823 patients with MG and 15,292 comparators from the general population, matched for age, sex and region of residence. Over a mean of 5.4 (standard deviation [SD] 3.8) years, a 39% increased risk of severe infection (ie, primary diagnosis on hospital or emergency records) was found for MG (72.5 vs 35.0 per 1000person-years; adjusted hazard ratio [AHR] of 1.39, 95% CI 1.28-1.51). The most common types of infections diagnosed in patients with MG were all-cause respiratory infections (21.6%), bacterial pneumonia (15.8%), skin/soft tissue infections (9.6%) and septicemia (6.7%). Risk factors for infection amongst patients with MG were rurality, chronic obstructive pulmonary disease (COPD), hypertension, prior infection, frailty and comorbidity burden. The second longitudinal study used the TNHIRD to compare the incidence of tuberculosis between 2317 patients with MG and 23,170 age-, sex- and comorbidity-matched controls (Ou et al, 2013). The study period was between 2000 and 2006 and the median follow-up over 3 years. Incidence of tuberculosis was higher in MG than in the comparator group (29.2 vs. 13.3 per 10,000person-years; AHR of 1.96, 95% CI 1.22-3.16) and most patients had pulmonary tuberculosis. Risk factors for tuberculosis amongst patients with MG were, an age of 60 or more and use of corticosteroids. Presence of thymoma, prior thymectomy, diabetes mellitus or COPD did not increase tuberculosis risk. Sipilä et al. investigated hospitalization trends in patients with MG between 2004 and 2014, using the national registry of Finland (Sipila et al, 2019). Eight hundred and sixty-one patients with MG had a total of 2989 hospital admissions and the proportion of infections as primary diagnosis increased from 4.5% to 10.4% during the study period. The most common diagnoses were lower respiratory tract infections (N=65/240, 27.1%), septicemia (N=36/240, 15%) and urinary tract infections (N=18/240, 7.5%). Finally, a study in China compared the infection rate post-thymectomy, between 53 patients with MG with early extubation and 43 patients with late extubation. The authors found a higher risk of postoperative pulmonary infection (39.5% vs. 11.3%, respectively) in patients with late extubation (Chen et al, 2019)

Part II Module SII Nonclinical part of the safety specification

Rozanolixizumab is a humanized immunoglobulin (Ig) G4 monoclonal antibody that selectively inhibits the activity of the neonatal Fc receptor for IgG (FcRn). The cynomolgus monkey and rhesus monkey were considered the pharmacologically relevant species to assess toxicity of rozanolixizumab. Key safety findings from nonclinical studies and relevance to human usage are presented below.

SII.1 Toxicology

SII.1.1 Single and multiple dose toxicity studies

The toxicology assessment of rozanolixizumab includes a Good Laboratory Practice (GLP) compliant 4-week intravenous (iv) and subcutaneous (sc) toxicity study with an 8-week, treatment-free recovery period in cynomolgus monkeys, an in vitro tissue cross-reactivity study with human and cynomolgus monkey tissues, and a GLP-compliant 13-week iv and sc toxicity study in cynomolgus monkeys with an 8-week treatment-free recovery period. There were no adverse findings, including no clinical signs, and the total plasma IgG levels decreased by approximately 60% to 90% (from the lowest predose value) at the high dose levels. The No Observed Adverse Effect Level was 150mg/kg every 3 days (the highest dose and dosing frequency tested) via both the iv and sc routes. In the tissue cross-reactivity study, binding of rozanolixizumab to both human and cynomolgus monkey tissues was similar, with the expected staining observed predominantly in cells known to express FcRn. This binding had no toxicological consequence in vivo as evidenced by the lack of adverse effects observed in the toxicology studies in cynomolgus monkeys.

A GLP-compliant 26-week sc toxicity study in sexually-mature cynomolgus monkeys with an 8-week recovery was conducted to assess fertility endpoints and to support long-term administration of rozanolixizumab and to support market authorization. The study included a vehicle control group and a high dose sc rozanolixizumab dosing group (150mg/kg every 3 days). Rozanolixizumab was well tolerated during chronic dosing at 150mg/kg sc, there were no observed adverse effects resulting from pharmacological effects or any off-target toxicity.

Meningeal infiltrates and perivascular cuffing of mononuclear inflammatory cells in the cerebral parenchyma were observed at minimal magnitude and without any observed glial activation or neuronal damage in part of the animals of the 13-week study. However, the overall incidence was not different across groups, including controls and in rozanolixizumab-treated animals, there was no apparent relationship with immunogenicity or loss of PD and there were no associated clinical signs such as neurobehavioral effects or signs of infection or inflammation. These observations of meningeal infiltrates and perivascular cuffing in the cerebral parenchyma are common spontaneous findings in cynomolgus monkeys of various origin (Chamanza et al, 2010; Butt et al, 2015).

Relevance to human: The lack of adverse findings due to rozanolixizumab pharmacology at a substantial margin over the expected clinical exposure supports the clinical use of rozanolixizumab. Meningeal infiltrates and perivascular cuffing in the cerebral parenchyma of monkeys in the 13-week toxicology study are common spontaneous findings in the cynomolgus monkey with no relationship to rozanolixizumab's mechanism of action. FcRn appears not to be involved in the efflux of IgG from the brain and therefore, inhibition of IgG binding to FcRn will

not result in the accumulation of pathological IgG and inflammatory cells around the microvasculature of the brain and in choroid plexus.

SII.1.2 Genotoxicity and carcinogenicity

Rozanolixizumab has no genotoxic potential. It is comprised of native, nonmodified amino acids, does not contain any chemical linkers or chelators, and is catabolized into peptides and natural amino acids. In accordance with the International Council for Harmonisation (ICH) Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1) (ICH S6 [R1], 2011), genotoxicity studies have not been performed. Rozanolixizumab is also unlikely to cause any cellular signaling-related downstream promoting events and there is no evidence in the literature that FcRn function is related to hormonal regulation, apoptosis, or tumor cell migration and metastasis in humans. Decreased serum IgG has not been associated with increased cancer risk in humans. There is limited and conflicting evidence in the literature from experimental mouse models proposing a potential role for FcRn in antigen presentation to tumor-specific CD8+ T cells and natural killer (NK) cell in protective anti-tumor immunity. The overall weight of evidence from the literature suggests that rozanolixizumab would not be expected to have either any effect on oncogenic virus promotion or anti-tumor CD8+ T- and NK cells responses.

Four-week, 13-week and 26-week repeat dose toxicity studies in cynomolgus monkeys (a pharmacologically relevant species) showed a lack of effect on cellular immune function or signs of tissue hyperplasia or dysplasia, increased organ weight or cell proliferation, and no signs of lymphoproliferative changes, pre-cancerous or cancerous lesions.

Relevance to human: The chemical structure and mechanism of action of rozanolixizumab, together with the lack of proliferative findings in preclinical studies in a pharmacologically relevant animal species and the absence of effects on the immune cellular function indicate that it presents no additional risks for genotoxicity or carcinogenicity to humans.

SII.1.3 Reproductive/developmental toxicity

No rozanolixizumab related adverse effects were noted following histopathology of the male and female reproductive tracts in the 4-week, 13-week, and 26-week iv and sc general toxicity studies in cynomolgus monkeys. In the 26-week toxicity study in sexually mature animals, no effect of rozanolixizumab was observed on male reproductive endpoints (ejaculate weight, sperm count, sperm motility, or morphology). No effect of rozanolixizumab was also observed on female reproductive endpoints (menstrual cyclicity or ovarian/uterine maturation status). Reproductive hormone analyses were not performed due to the absence of rozanolixizumab related effects on male or female fertility endpoints.

An enhanced Pre- and Post-Natal Development study in cynomolgus monkeys, with dosing of rozanolixizumab from gestation day 20 to parturition, has been completed as recommended in ICH S6 (R1) and M3 (R2) guidelines (ICH S6 [R1], 2011; ICH M3 [R2], 2009). Subcutaneous administration of rozanolixizumab to pregnant cynomolgus monkeys every 3 days, from Gestation Day 20 up to delivery at dose levels of 50 or 150mg/kg, resulted in expected decreases in IgG, globulin and total protein levels and slight decreases in albumin in maternal animals. There were no effects on pregnancy outcome or postnatal development up to Postnatal Day 180±1 of surviving infants. No test item-related macroscopic or microscopic changes were observed in any stillborn, unscheduled sacrifice (moribund), or infants found dead. Offspring of

the high dose treated dams had very low levels of IgG at birth, as expected from the blockade of placental FcRn and the resulting blockade of maternal IgG transfer in utero. However, IgGs in infants from rozanolixizumab -treated mothers were within control range within 2 months.

Relevance to human: Cynomolgus monkey physiology allows the assessment of potential impact of rozanolixizumab on reproduction, development, and parturition in a human relevant model. The lack of findings outside of the expected pharmacological impact on circulating IgG supports the clinical use of rozanolixizumab. However, the lack of maternal IgG transfer in utero during active treatment should be factored in for the management of pregnancies and the risk of infant infection over the first weeks/months after birth.

SII.1.4 Local tolerance

Local tolerance was evaluated as part of repeat dose toxicity studies. Increased inflammatory cell infiltrates at the sc injection sites observed in some animals might reflect a local irritation effect of the test item formulation.

SII.1.5 Immunotoxicity

The overall exposure to rozanolixizumab and the pharmacodynamic (PD) effect of rozanolixizumab were maintained throughout the toxicity studies despite the development of antidrug antibodies in a significant number of animals. In some animals, this resulted in a loss of exposure to rozanolixizumab and a reduction in PD response. Two animals in the 26-week toxicity study showed signs of immune complex disease (ICD) in several organs (and this was considered adverse in 1 animal) as a consequence of the presence of antidrug antibodies. Immune complex disease does not generally appear in a dose-related manner and the translatability from animal studies to clinical studies is generally considered to be low (Vahle, 2018; Rojko et al, 2014).

The impact of rozanolixizumab on antibody B-cell and T-cell response to an antigen was investigated in the 13-week and 26-week toxicology studies using cynomolgus monkeys. A T-cell dependent antibody response (TDAR) assay was incorporated into the dosing phase of both studies and into the recovery phase of the 26-week study. The assay used Keyhole Limpet Haemocyanin (KLH) as an antigen to evaluate antibody response in the presence of rozanolixizumab. In both studies, rozanolixizumab treatment resulted in a reduced IgG response to KLH in the TDAR but did not affect the IgM response. A rechallenge with KLH during the treatment-free phase of the 26-week study, when rozanolixizumab was cleared, showed a restoration of the IgG response. This is consistent with the pharmacology of rozanolixizumab where IgM response would not be expected to be affected by inhibition of FcRn binding as IgM do not bind FcRn, but IgG would be cleared more rapidly during rozanolixizumab treatment.

There was no impact of rozanolixizumab on lymphoid cell populations or lymphoid organs architecture and cellularity in any of the toxicity studies conducted. The effect of rozanolixizumab was limited to the pharmacologically driven reduction in IgG levels.

Relevance to human: The lack of adverse findings on the immune system of the cynomolgus monkey due to rozanolixizumab at a substantial margin over the expected clinical exposure supports the clinical use of rozanolixizumab. The occurrence of ICD in 2 of the animals in toxicology studies is a consequence of immunogenicity and can be observed in animals with human or humanized biotherapeutics, especially at supratherapeutic doses, but is not related to

the dose, generally occurs randomly and has been shown of poor relevance to human. Therefore, it is considered as not relevant to any potential human response to rozanolixizumab treatment. Data indicate that rozanolixizumab treatment does not interfere with the adaptive immune system's response to an antigen and a normal response to a vaccine would be expected. Although the pharmacology of rozanolixizumab would mean that the IgG levels postvaccination would be substantially reduced while rozanolixizumab was present, they would return to normal values once rozanolixizumab was cleared.

SII.2 Safety pharmacology

No specific safety pharmacology studies were conducted. Safety pharmacology parameters were included within the 4-week and 13-week iv and sc general toxicity studies. No effects on electrocardiogram parameters and waveform or morphology were seen, there were no effects on heart rate or blood pressure after repeat dose. Respiratory rate and depth were recorded and neurological observations (Functional Observational Battery, modified for non-human primates) were performed. No adverse effects on any of the measured parameters at any time point, at any dose level in either study as a result of rozanolixizumab treatment were observed.

SII.3 Other toxicity-related information and data

SII.3.1 Tissue cross reactivity study and ex vivo evaluation of rozanolixizumab effects on the human intestinal tract applying the InTESTineTM model

In a tissue cross-reactivity study, binding of rozanolixizumab to both human and cynomolgus monkey tissues was generally similar with the expected staining observed predominantly in cells known to express FcRn, with no unexpected off-target binding.

To investigate the GI adverse events (AEs) observed in the first-in-human study, an ex vivo 2-compartmental model using human intestinal tissue segments was used to determine any effect of the rozanolixizumab batch used in the first in human study (added to apical or basolateral compartment) on the tissue viability, permeability, and histology, and to evaluate rozanolixizumab-mediated changes in the release of a panel of eicosanoid lipid mediators identified from literature as potential biomarkers of GI injury or homeostasis. Data collected did not show any significant changes induced by rozanolixizumab on human GI tissue when tested at the clinically relevant concentrations.

SII.3.2 Cytokine release studies in vitro

The potential of rozanolixizumab to stimulate cytokine release was assessed in different human in vitro settings using whole human blood, peripheral blood mononuclear cells, umbilical blood vein endothelial cells (HUVEC) confirmed to express FcRn or a combination of blood cells and HUVEC, and rozanolixizumab in a soluble, immobilized, or crosslinked format. The anti-human CD52 antibody alemtuzumab and the anti-human CD3 antibody muronomab served as positive controls, and an isotype matched control as negative agent. None of the assay configurations resulted in cytokine release with rozanolixizumab, suggesting that headaches and GI effects seen after iv administration in human participants treated with rozanolixizumab were not related to cytokine release.

SII.3.3 Investigative assessment of the potential cross reactivity with a selected panel of human and cynomolgus monkey brain tissues

Although the tissue cross-reactivity showed similar binding pattern of rozanolixizumab to human and cynomolgus monkey tissues with the expected staining and no clinical signs were observed in toxicology studies, headaches occurred in the first in human study. More detailed cross-reactivity on brain tissue from human and cynomolgus monkey was evaluated to investigate whether any differences in tissue staining may explain differences in the response between the two species. Only small inter-species differences in the quantity, but not quality, of the specific immunohistochemical signal were observed in microvascular endothelial cells of the central nervous system (more intensive in cynomolgus monkey). These differences are unlikely accountable for the clinical inter-species differences observed between cynomolgus monkey and human.

Part II Module SIII Clinical trial exposure

Phase 3 rozanolixizumab studies in gMG indication were combined for the purpose of pooled safety analyses.

Pool S1 contains all rozanolixizumab-treated study participants with at least 1 treatment cycle. Double-blind MG0003 study data and open-label extension (OLE) MG0004 (only data from the initial 6 weeks) and MG0007 data were combined for each study participant. The pool S1 was mainly used to characterize the study duration.

Pool S2 is the main safety pool and is used to assess the safety of repeated symptom-driven cycles. Pool S2 is a subset of Pool S1, in which data from MG0004 is not utilized due to lack of a treatment-free follow-up period immediately following the initial 6 weeks of treatment.

For the clinical study exposure calculation, safety Pool S1 is utilized. The Phase 3 gMG exposure data (Pool S1) has been updated based on the completed MG0007 study.

Table Part II–2 presents the study participant exposure to rozanolixizumab in Phase 3 gMG clinical studies by duration of time within studies and overall participant-time in years.

Table Part II–2: Duration of exposure (duration of time in studies from Pool S1)

Duration of exposure	Study participants (%)	Participant-years
Indication: MG		
>0 months	196 (100%)	
>6 months	154 (78.6%)	
>12 months	136 (69.4%)	
Total participant time	-	327.55

MG=myasthenia gravis
Data source: Module 5.3.5.3, RMP Exposure (MAA) Table 1
Footnote: exposure is presented for total rozanolixizumab treatment groups (≈7mg/kg and ≈10mg/kg)

Table Part II–3 presents study participant exposure to rozanolixizumab in Phase 3 gMG clinical studies by age group and gender.

Table Part II–3: Exposure by age group and gender (Pool S1)

Age group (years)	Study participants		Participant-years	
	Male	Female	Male	Female
<18	0	0	0	0
≥18 to <65	48	100	86.65	169.06
≥ 65 to <85	31	15	45.41	21.61
≥85	0	2	0	4.83
Total	79	117	132.05	195.49

Data source: Module 5.3.5.3, RMP Exposure (MAA) Table 2
Footnote: exposure is presented for total rozanolixizumab treatment groups (≈7mg/kg and ≈10mg/kg)

Table Part II–4 presents study participant exposure to rozanolixizumab in Phase 3 gMG clinical studies by dose.

Table Part II–4: Exposure by dose (Pool S1)

Dose of exposure	Study participants	Participant-years
Rozanolixizumab ≈7mg/kg	139	155.87
Rozanolixizumab ≈10mg/kg	146	171.68
Total	196	327.55

Data source: Module 5.3.5.3, RMP Exposure (MAA) Table 1

Table Part II–5 presents study participant exposure to rozanolixizumab in Phase 3 gMG clinical studies by ethnic origin.

Table Part II–5: Exposure by ethnic origin (Pool S1)

Ethnic origin	Study participants	Participant-years
Black	5	7.45
White	132	215.34
Asian	21	39.04
Native Hawaiian or other Pacific Islander	1	2.22
Unknown[a]	37	63.49
Total	196	327.55

Data source: Module 5.3.5.3, RMP Exposure (MAA) Table 3
Footnote: exposure is presented for total rozanolixizumab treatment groups (≈7mg/kg and ≈10mg/kg)
[a] Race and ethnicity are prohibited to collect in France and Canada.

Part II Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria in pivotal clinical studies within the development programme are discussed in Table Part II–6 below:

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Pediatrics (patients under 18 years of age)	
Reason for exclusion	Considering the proposed indication and GCP, it is a standard practice to initiate studies in adult patient population. The safety and efficacy of rozanolixizumab in the pediatric population have not been established.
Is it considered to be included as a missing information	No
Rationale	No efficacy and safety data in study participants under 18 years are available to support the initial submission. Use in pediatrics is not considered a part of the proposed indication population. Thus, use in pediatrics is not considered a missing information as per EU GVP module V rev 2. Paediatric studies are planned under a separate PIP (EMEA-002681-PIP01-19).
Pregnancy	
Reason for Exclusion	Limited data does not allow to draw conclusion on the use of rozanolixizumab in pregnant women. Considering GCP, it is a standard practice to exclude pregnant women from clinical studies.
Is it considered to be included as a missing information	Yes
Breastfeeding	
Reason for Exclusion	It is unknown whether rozanolixizumab is excreted in human milk. Considering GCP, it is a standard practice to exclude lactating women from clinical studies.
Is it considered to be included as a missing information	No
Rationale	Lactation is properly addressed in the relevant sections of the SmPC and Package Leaflet.
Live vaccination	
Reason for Exclusion	The safety of immunization with live or live-attenuated vaccines is currently unknown. No clinical data are available on the potential for transmission of infection by live vaccines.

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Is it considered to be included as a missing information	No
Rationale	Given the cyclic nature of rozanolixizumab's dosing, participants will have the opportunity to get vaccines between cycles. Information on this topic is included in the relevant sections of the SmPC and Package Leaflet.
Hypersensitivity (to rozanolixizumab, or any of the excipients)	
Reason for Exclusion	All mAbs could potentially be associated with hypersensitivity reactions, including anaphylactic events.
Is it considered to be included as a missing information	No
Rationale	Nonserious hypersensitivity reactions is a potential risk that does not have an important impact on the risk-benefit profile and does not meet the criteria for important risk per the EU-GVP module V rev2 definition. Serious hypersensitivity reactions are managed through routine risk minimization SmPC recommendations.
Hyperprolinemia	
Reason for Exclusion	250mM L-proline is used in rozanolixizumab formulation as stabilizing agent.
Is it considered to be included as a missing information	No
Rationale	Information about use of proline as an excipient is included in the relevant sections of the SmPC and Package Leaflet.
Clinically relevant active infection (eg, sepsis, pneumonia or abscess), or history of serious infection	
Reason for Exclusion	There is a potential concern that rozanolixizumab may increase the risk of infection based on its mode of action.
Is it considered to be included as a missing information	No
Rationale	Serious infection is considered an important potential risk with rozanolixizumab.
Known TB infection, at high risk of acquiring TB infection, or latent TB infection, or current/history of nontuberculous mycobacterial infection	

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Reason for exclusion	Based on the current scientific knowledge, the immune response to TB is T-cell dependent (Kaufmann, 2002) and there is currently no clear data supporting a significant role of the humoral immune response to control the tuberculosis infection. (De Martino et al, 2019). Inhibition of FcRn by rozanolixizumab is not expected to affect plasma cells, B-cell repertoire, or memory B cells, or to interfere with other cells of the innate and adaptive immune systems or complement. However, immunocompromised participants concomitantly receiving other immunosuppressive drugs could be at a higher risk of developing TB infection and therefore will not be eligible to participate/complete the study. The exclusion was introduced to minimize effect of confounding factors.
Is it considered to be included as missing information	No
Rationale	Serious infection is considered an important potential risk with rozanolixizumab.
Concurrent acute or chronic hepatitis B or C or HIV	
Reason for exclusion	Immunoglobulin G plays a major role in viral neutralization (Walker et al, 2020; Warner et al, 2020). Treatment with rozanolixizumab could potentially precipitate viral reactivation.
Is it considered to be included as missing information	No
Rationale	Serious infection is considered an important potential risk with rozanolixizumab.
Unstable liver or biliary disease and/or ALT/AST >3.0xULN	
Reason for exclusion	Participants with unstable hepatobiliary disease at entry could confound the recognition and risk assessment of PDILI during clinical trial (Treem et al, 2021).
Is it considered to be included as missing information	No
Rationale	No dedicated studies have been conducted in patients with hepatic impairment. Human mAbs such as rozanolixizumab are expected to be catabolized by degradation to small peptides and amino acids, which are expected to be excreted or recycled in the same manner as endogenous IgG. As a result, hepatic impairment is not expected to affect the pharmacokinetics of rozanolixizumab. Based on a population pharmacokinetic analysis, hepatic biochemical and function biomarkers (ALT, AST, alkaline phosphatase and bilirubin) had no significant effect on rozanolixizumab apparent clearance.
Renal impairment (eGFR <45mL/min/1.73m^2)	

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Reason for exclusion	The threshold was introduced following interactions with the Regulatory Agencies.
Is it considered to be included as missing information	No
Rationale	No dedicated studies have been conducted in patients with renal impairment, which is in accordance with regulatory guidance. Rozanolixizumab is a mAb and is not expected to undergo renal elimination or excretion due to its large molecular size, and therefore renal impairment is not expected to affect the pharmacokinetics of rozanolixizumab. A population pharmacokinetic-pharmacodynamic analysis, which included participants with mild and moderate renal impairment, eGFR (range: 38.2 to 161mL/min/1.73m^2) did not reveal any significant impact on rozanolixizumab apparent clearance. Also, mild or moderate renal impairment did not affect the overall safety profile in participants with gMG.
Active neoplastic disease or history of neoplastic disease	
Reason for exclusion	Immunomodulatory compounds may theoretically interfere with the pathogenesis of malignancy.
Is it considered to be included as missing information	No
Rationale	The chemical structure and mechanism of action of rozanolixizumab, together with the lack of proliferative findings in preclinical studies in a pharmacologically relevant animal species and the absence of effects on the immune cellular function indicate that it presents no additional risks for genotoxicity or carcinogenicity to clinical subjects (see Section SII.1.2).
Neutrophil abnormalities (ANC <1500 cells/mm^3)	
Reason for exclusion	Patients with MG may concomitantly receive other immunosuppressive that may induce neutropenia which in combination with low IgG level may increase the risk of infection.
Is it considered to be included as missing information	No
Rationale	Neutropenia results in compromised immunity and increases the susceptibility to infections. Serious infection is considered an important potential risk with rozanolixizumab.
Low IgG level (serum total IgG level ≤5.5g/L)	
Reason for exclusion	Rozanolixizumab at the doses used in MG0003 was expected to reduce IgG levels by approximately 70-80% by the end of Treatment Period. Low IgG levels may increase the risk of infection.

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Is it considered to be included as missing information	No
Rationale	Serious infection is considered an important potential risk with rozanolixizumab.
Active GI disorders: IBD, or GI ulceration or diverticulitis	
Reason for exclusion	Gastrointestinal disturbances such as diarrhea, nausea and vomiting were observed at a higher frequency amongst the study participants treated with rozanolixizumab. These adverse events may worsen preexisting active GI disorders.
Is it considered to be included as missing information	No
Rationale	Diarrhea is included as ADR in the relevant labelling sections.
IgA deficiency and or current or medical history of primary immunodeficiency	
Reason for exclusion	Immunodeficiencies have potential mechanistic similarities (eg, inducing transient reduction in IgG) to those induced by an FcRn inhibitor. Participants with IgA deficiency in addition to reduced IgG levels may be at an increased risk of developing infections.
Is it considered to be included as missing information	No
Rationale	The risk of infection is addressed as part of the important potential risk of serious infections.
History of solid organ transplant or hematopoietic stem cell/marrow transplant	
Reason for exclusion	To comply with GCP and minimize effect of confounding factors (immunosuppressive treatment) on safety evaluations as well as not to compromise such a patient's health (susceptibility to infections).
Is it considered to be included as missing information	No
Rationale	These categories of patients have a compromised immunity and are at the increased risk of infections. The risk of infection is addressed as part of the important potential risk of serious infections.
Prior and concomitant treatment with immunosuppressive drug including rituximab and biologicals	
Reason for exclusion	To minimize a carryover effect or potential drug-drug interaction which could interfere with efficacy analysis and further compromise patients' immune system making them susceptible to infections.

Table Part II–6: Exclusion criteria in pivotal clinical studies within the development program

Is it considered to be included as missing information	No
Rationale	Concomitant use of rozanolixizumab with immunosuppressive drugs could further compromise immunity and increase the susceptibility to infections. The risk of infection is addressed as part of the important potential risk of serious infections. Assessment of infections will include stratification analysis of immunosuppressive drugs used concomitantly. Additionally, as rozanolixizumab interferes with the FcRn recycling mechanism of IgG, the serum concentrations of IgG-based medicinal products (eg, mAbs and IVIg) and Fc–peptide fusion proteins are expected to be decreased if administered concomitantly. Information on potential drug-drug interaction with a recommendation for prescribers on concomitant use of such medicinal products is included in the relevant sections of the SmPC and Package Leaflet.
Study participant has a lifetime history of suicide attempt or had suicidal ideation in the past 6 months	
Reason for exclusion	Patients with a history of suicide attempt or suicidal ideation in the past 6 months are at an increased risk of suicidality; therefore, these participants were excluded to avoid interference with safety assessments.
Is it considered to be included as missing information	No
Rationale	Based on mechanism of action, size of mAb, and clinical data, it is not expected that rozanolixizumab can trigger or worsen suicidal ideation/suicidality.

ADR=adverse drug reaction; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; EU GVP=European Union Good Pharmacovigilance Practice; eGFR=estimated glomerular filtration rate; FcRn=neonatal Fc receptor; FDA=Food and Drug Administration; GCP=Good Clinical Practice; GI=gastrointestinal; HIV=human immunodeficiency virus; IBD= inflammatory bowel disease; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; mAb=monoclonal antibody; MG=myasthenia gravis; PDILI=potential drug-induced liver injury; PIP=pediatric investigation plan; PK=pharmacokinetics; SmPC=Summary of Product Characteristics; TB=tuberculosis; ULN=upper limit normal

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.2.1 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table Part II–7 provides an example of overview of exposure in special population typically under-represented in clinical trial development programmes.

Table Part II–7: Exposure of special populations included or not in clinical trial development programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td>Pregnant women were not included in the clinical development program. In the entire MG development program, 1 pregnancy was reported in MG0004 after maternal exposure to rozanolixizumab during the first trimester that resulted in a birth of a healthy child.</td></tr>
<tr><td>Breastfeeding woman</td><td>Not included in the clinical development program.</td></tr>
<tr><td>Patients with relevant comorbidities:
• Patients with renal impairment</td><td>Participants with eGFR of ≥45mL/min/1.73m^2 were permitted in the study. The effect of renal impairment on the incidence of TEAE categories was evaluated in MG0003 and Pool S2. The participants per degree of renal impairment were:
<table>
<tr><td colspan="6">MG0003</td><td colspan="3">Pool S2</td></tr>
<tr><td colspan="3">Placebo
N=67</td><td colspan="3">RLZ Total[a]
N=133</td><td colspan="3">RLZ Total[a]
N=188</td></tr>
<tr><td colspan="9">mL/min/1.73m^2</td></tr>
<tr><td>≥90</td><td>60–89</td><td>30–59</td><td>≥90</td><td>60–89</td><td>30–59</td><td>≥90</td><td>60–89</td><td>30–59</td></tr>
<tr><td>n=42</td><td>n=22</td><td>n=3</td><td>n=89</td><td>n=37</td><td>n=6</td><td>n=122</td><td>n=57</td><td>n=8</td></tr>
</table>
[a] The RLZ totals for MG0003 and Pool S2 include 1 participant with missing eGFR.
In MG0003 and Pool S2, there were no clear trends in the incidences of TEAE categories by eGFR subgroup; although interpretation is limited by the low number of participants in the 30-59mL/min/1.73m^2. The most common TEAEs were consistent between the ≥90mL/min/1.73m^2 and the 60-89mL/min/1.73m^2 subgroups in MG0003 (headache, diarrhoea, and pyrexia) and in Pool S2 (headache and diarrhoea). The only events to occur in ≥2 participants in the 30-<60mL/min/1.73m^2 subgroup were diarrhoea, arthralgia, and renal impairment (Module 2.7.4; ISS Table 7.4.1.4.1 and Table 7.2.2.1.4). Two TEAEs of renal impairment were nonserious and reported as not resolved. One of the participants who had a mild eGFR decrease during observation period, was overweight and had a medical history of Type 2 diabetes mellitus, and hypertension. The second participant with a moderate renal impairment had fluctuation of eGFR values during treatment period. Both participants had mildly elevated creatinine at Baseline and most of the time throughout the study.</td></tr>
<tr><td>Patients with other relevant comorbidities:
Patients with hepatic impairment
Patients with cardiovascular impairment</td><td>Not included in the clinical development program.</td></tr>
</table>

Table Part II–7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	The effect of race on the incidence of TEAE categories was evaluated in MG0003 and Pool S2. The populations in both MG0003 and Pool S2 were predominantly in the White subgroup, therefore subgroup analysis by race is limited. Please refer to EU RMP Section Part II Module SIII for the exposure by ethnic origin. Overall, there were no clear trends in the incidences of TEAE categories by race subgroup. Additionally, there were no significant differences in rozanolixizumab PK or PD (total IgG and anti-AChR) between Asian and non-Asian participants in the population PK-PD modelling (Module 2.7.2, Section 3.3.3). Phase 1 clinical study UP0060 was a randomized, participant-blind, investigator-blind, placebo controlled, single ascending dose, cohort design to compare the safety, tolerability, and PK of rozanolixizumab, and to explore the PD of rozanolixizumab administered by sc infusion in 64 healthy male and female study participants, including 22 Japanese, 20 Chinese, and 22 Caucasian study participants. Rozanolixizumab was found to be generally tolerated with an acceptable safety profile after single sc administration of 4mg/kg, 7mg/kg, and 10mg/kg doses in Japanese, Chinese, and Caucasian study participants. Overall, there were no unexpected findings in this study for the observed PK profile and PK parameters for rozanolixizumab at doses of 4mg/kg, 7mg/kg, and 10mg/kg across all ethnic groups. Dose dependent reductions in IgG and IgG subclasses were observed following administration of rozanolixizumab in Japanese, Chinese, and Caucasian study participants. Overall, the mean value of albumin remained within the normal range over time, and no clinically relevant changes from Baseline were observed.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

AChR=acetylcholine receptor; eGFR=estimated glomerular filtration rate; IgG=immunoglobulin G; ISS=Integrated Summary of Safety; PD=pharmacodynamics; PK= pharmacokinetics; sc=subcutaneous; RMP=Risk Minimization Plan; TEAE=treatment emergent adverse events

Part II Module SV Postauthorization experience

SV.1 Post-authorisation exposure

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment and completed a full cycle. Per Company core data sheet, a treatment cycle consists of 1 dose per week for 6 weeks administered via the subcutaneous route. One dose (infusion) is equal to 2 vials.

Cumulative patient exposure is estimated using the available UCB sales data from 01 Jul 2023 to 30 Jun 2024. Note that sales data are only available to UCB on a month-to-month basis.

The total amount of product sold is [redacted] which equals to [redacted] vials cumulatively as derived from the UCB sales data reported. For the calculation purposes, treatment cycles are defined as below.

$$\text{Treatment cycles (based on number of vials sold)} = \frac{\text{total amount of vials distributed}}{2^{*} \times 6^{**}}$$

* 2 vials are estimated to be used per infusion
** 6 is the number of infusions per cycle

According to this methodology, the cumulative patient exposure to rozanolixizumab is estimated at approximately [redacted] treatment cycles. The breakdown of the exposure by region is presented for the current/cumulative reporting intervals in Table Part II–8.

Table Part II–8: Patient exposure by region for the cumulative interval 01 Jul 2023 to 30 Jun 2024

Region	Country	Treatment cycles for the cumulative reporting interval
Europe/EEA	[redacted]	[redacted]
	[redacted]	[redacted]
APAC	[redacted]	[redacted]
US & Canada	[redacted]	[redacted]
Total count		[redacted]

APAC=Asia-Pacific; EEA=European Economic Area

Part II Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Based on the characteristics and target population of this drug, no evidence to suggest a potential for drug abuse or misuse is anticipated.

Part II Module SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Table Part II–9: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for non-inclusion in list of safety concerns
Headache	Headache is a common adverse reaction with rozanolixizumab, with the majority of headaches being mild in intensity. Headaches reported with rozanolixizumab, including severe events, have short duration and are in general manageable with nonopioid analgesia. Therefore, headache does not meet the criteria for important risk per the EU-GVP module V rev2 definition.
Gastrointestinal disturbances	Based on the incidence and severity of GI disturbances (eg, nausea, vomiting, diarrhea) observed to date this risk is not considered to affect the risk-benefit balance of the product given the severity of the intended indication and does not meet the criteria for important risk per the EU-GVP module V rev2 definition.
Local tolerability and injection site reaction	The incidence and severity of injection site reactions in clinical studies to date has been low and mild. Injection site reactions are therefore not anticipated to affect the risk-benefit balance of the product or have implications for public health.
Nonserious Infections	Nonserious Infections is a potential risk associated with the mode of action and does not have an important impact on the risk-benefit profile and does not meet the criteria for important risk per the EU-GVP module V rev2 definition. Serious infections is considered an important potential risk (see Table Part II–12).
Hypersensitivity reactions	Hypersensitivity reactions are a recognized risk for mAbs. The immunogenic potential of rozanolixizumab is expected to be low risk, based on structure, target characteristics, mechanism of action, and immunomodulatory properties. Overall, nonserious hypersensitivity reactions is a potential risk that does not have an important impact on the risk-benefit profile and does not meet the criteria for important risk per the EU-GVP module V rev2 definition. Serious hypersensitivity reactions are managed through routine risk minimization SmPC recommendations.
Reduction in albumin	No clinically significant changes in albumin have been observed in clinical trials with rozanolixizumab. Reversible, small decreases in mean protein levels (predominantly within normal limit) have been observed, which relate to the reduction in IgG levels and is anticipated with rozanolixizumab treatment.

Table Part II–9: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for non-inclusion in list of safety concerns
Thrombocytopenia	Across the rozanolixizumab development program, reductions in platelets counts without clinical consequences have been observed following rozanolixizumab administration, with evidence of positive dechallenge and rechallenge. These reductions in platelets counts do not have an important impact on the risk-benefit profile and do not meet the criteria for important risk per the EU-GVP module V rev2 definition.

ADR=adverse drug reaction; CTCAE=Common Terminology Criteria for Adverse Events; EU-GVP=European Union Good Pharmacovigilance Practice; GI=gastrointestinal; IgG=immunoglobulin G; IMP=investigational medicinal product; mAb=monoclonal antibody; RMP=risk management plan; SmPC=summary of product characteristics

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table Part II–10: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks	
Aseptic meningitis (Drug-induced aseptic meningitis [DIAM])	
Risk-benefit impact	The mechanism of DIAM with rozanolixizumab is unknown. To date, a single report of DIAM has been received in Phase 3 gMG program. Two additional reports of DIAM were received from the ongoing double-blind placebo-controlled study in the myelin oligodendrocyte glycoprotein associated disease indication The clinical management and the evolution of DIAM is different from other categories of meningitis, with usually a good prognosis, with a rapid recovery upon discontinuation of the drug, and with a possibility of reinitiating treatment. Serious events of aseptic meningitis have been reported. If symptoms are consistent with aseptic meningitis develop, diagnostic workup and treatment should be initiated according to the standard of care. In the SmPC (Section 4.4), a warning and precaution is included to minimize the risk of aseptic meningitis.
Important potential risks	
Serious infections	
Risk-benefit impact	Immunoglobulin of class G play a role in protection against infections. Based on its mechanism of action, rozanolixizumab may increase susceptibility to infections. From nonclinical toxicology repeat-dose studies, the pharmacodynamic effect of sustained suppression of IgG following rozanolixizumab treatment at supratherapeutic doses in the cynomolgus monkey did not result in increased infections in the treated animals. Treatment-emergent adverse events of infection were observed in the clinical trials with rozanolixizumab. In the SmPC (Section 4.4), a warning and precaution is included to minimize the risk of clinically important active infections. Serious infections may require medical intervention to be treated, including hospitalization.

Table Part II–10: Risks considered important for inclusion in the list of safety concerns in the RMP

Missing information	
Use during pregnancy	
Risk-benefit impact	There are limited data from the use of rozanolixizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development. Placental transfer of IgG and rozanolixizumab itself was affected, with very low levels of IgG at birth in offspring from treated mothers and rozanolixizumab being detected only transiently in offspring from the high dose group. Use during pregnancy is considered missing information with rozanolixizumab. A recommendation is included in the SmPC (Section 4.6), to minimize the untoward effect of rozanolixizumab on fertility, pregnancy and lactation.
Long-term safety	
Risk-benefit impact	Limited data are available on long-term use of rozanolixizumab in adult patients with gMG. The available evidence in gMG and other indications is not suggestive for a different safety profile compared to short term use. Further data are being collected in the ongoing clinical development program.

DIAM=drug-induced aseptic meningitis; FcRn=neonatal Fc receptor; gMG=generalized myasthenia gravis; IgG=immunoglobulin G; RMP=risk minimization plan; SmPC=summary of product characteristics;

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns were identified or reclassified as part of this updated RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risks

Important identified risks with rozanolixizumab treatment are characterized in the table below.

Table Part II–11: Important identified risk: Aseptic meningitis (Drug-induced aseptic meningitis)

Potential mechanisms	Aseptic meningitis refers to clinical and laboratory evidence for meningeal inflammation with negative cerebrospinal fluid bacterial cultures. Drug-induced aseptic meningitis is observed with IVIg therapies, monoclonal antibodies, non-steroidal anti-inflammatory drugs, and antibiotics (Yelehe-Okouma et al, 2018; Vulsteke et al, 2010). Drug-induced aseptic meningitis can be caused by a direct toxicity of the administered drug, immunological (hypersensitivity) reaction, or as in the cases with Igs by a high dose of IVIg (Kretowska-Grunwald et al, 2022) or preparations containing higher proportions of IgA. Overall, the exact etiology of aseptic meningitis can only be identified in 30-65% of the cases.

Table Part II–11: Important identified risk: Aseptic meningitis (Drug-induced aseptic meningitis)

	Aseptic meningitis has also been observed in MG patients treated with IVIg (Kretowska-Grunwald et al, 2022). A mechanism by which rozanolixizumab would cause aseptic meningitis is not known. Rozanolixizumab is a humanized IgG4 with a low intrinsic immunogenicity. No induction of cytokine release was observed in vitro study (Study Report 40001817). It is very unlikely to induce inflammation and tissue damage through interactions with Fc gamma receptors or through the complement pathway on immune cells. The inhibition of systemic FcRn will result in a decrease of systemic and brain levels of IgGs. Different in vivo and in vitro models have demonstrated that FcRn present in the blood brain barrier can be expected to play only a limited role in IgG transcytosis, if any (Ruano-Salguero and Lee, 2020; Chen et al, 2014; Abuqayyas and Balthasar, 2013; Garg and Balthasar, 2009). Therefore, the blockade of FcRn is not likely to have an effect on IgG efflux from the brain. The presence of rozanolixizumab in brain tissue is not expected to induce inflammation. Although infiltration of inflammatory cells in meninges or in the brain parenchyma were observed in 1 specific nonclinical study, they were classified as background findings (See Section Part II Module SII).
Evidence source(s) and strength of evidence	Data to evaluate safety concern derived from clinical studies and post marketing data.
Characterization of the risk	**Frequency:** One patient with gMG experienced DIAM following the first dose of ≈10mg/kg dose in MG0007, within 72 hours (1/239 participants treated with rozanolixizumab in the gMG Phase 2 and Phase 3 clinical program). This patient received placebo treatment in double-blind, placebo controlled MG0003 study. **Severity:** The event in MG0007 was severe. **Reversibility:** The event in MG0007 occurred within 72 hours of a first administration of rozanolixizumab and resolved without sequelae following treatment discontinuation. **Other indications**: A further 2 cases were reported in participants with [redacted] an ongoing double-blind, placebo-controlled study. The 2 events were serious and moderate in intensity. The events occurred within 72 hours of a first administration of blinded treatment and resolved without sequelae following treatment discontinuation. **Post marketing data**: Based on the review of global pharmacovigilance data until 25 Dec 2023, cases of aseptic meningitis have been reported in post marketing at the EU recommended dose of ≈7mg/kg.
	Long term outcome/ impact on quality of life: In general, prognosis of DIAM is favorable with spontaneous recovery after stopping the suspected drug, without sequelae and with a possibility of reinitiating treatment. No long-term effects

Table Part II–11: Important identified risk: Aseptic meningitis (Drug-induced aseptic meningitis)

	following a resolution of the event are expected (Bihan et al, 2019; Lockwood and Carr, 2014).
Absolute risk	The incidence of aseptic meningitis observed with IVIg and monoclonal antibody treatments represents up to 0.067% of all infusions (Kretowska-Grunwald et al, 2022) but can occur in 0.6-1% of patients treated with IVIg (Guo et al, 2018). Based on epidemiological studies and real-world evidence, no population-based estimates of DIAM are available, in the general population, in the gMG population, or in other indications currently being pursued for rozanolixizumab. Bharath et al, 2014 retrospectively reviewed all cases of IVIg-associated adverse transfusion reactions at the London Health Sciences Centre from Jan 2008 to Dec 2013 to identify cases of IVIg-induced aseptic meningitis. Eight of 1324 (0.60%; 95% CI 0.3065%-1.188%) patients who received IVIg infusions had aseptic meningitis. In another study, of 54 patients receiving high dose IVIg for immune neuromuscular disease, 6 developed aseptic meningitis confirmed by CSF analysis. Preexisting migraine is a risk factor associated with a higher incidence of the event (Sekul et al, 1994).
Risk factors and risk groups	Drug-induced aseptic meningitis is an uncommon complication of unknown etiology with IVIg and some therapeutic antibodies that seems to affect all ages, however with a tendency toward higher incidence with higher dose (Yelehe-Okouma et al, 2018; Bharath et al, 2014; Vulsteke et al, 2010). Chronic migraine and autoimmune diseases could be predisposing factors for DIAM, given the experience seen with IVIg (Yelehe-Okouma et al, 2018, Sekul et al, 1994).
Preventability	Prehydration and good fluid intake may be beneficial in preventing or reducing the incidence of drug induced aseptic meningitis. In patients who experienced drug induced aseptic meningitis during prior infusions, acetaminophen and antihistamines can be given as a premedication therapy (Cherin et al 2016). However, evidence for preventative measures is limited. During rozanolixizumab treatment, it is recommended to monitor for signs of aseptic meningitis and perform diagnostic workup and treatment if necessary (SmPC Section 4.4). Aseptic meningitis (DIAM) is also included in SmPC Section 4.8 (Undesirable effects).
Impact on risk-benefit balance of the product	Given the unmet need, the demonstrated benefit of rozanolixizumab, the rarity of the event in the gMG development program (1/239 participants treated with rozanolixizumab in the gMG Phase 2 and Phase 3 clinical program), and the resolution of the event without sequelae, it has been considered that despite the risk of aseptic meningitis, the overall benefit-risk balance remaining positive. Routine and additional pharmacovigilance will be implemented to monitor aseptic meningitis (see Part III). Aseptic meningitis is included in Warnings and Precautions (SmPC Section 4.4) and in Undesirable effects (SmPC Section 4.8). Risk minimization activities are discussed in Part V.
Public health impact	Based on overall low incidence and good prognosis of DIAM, no significant public health impact is expected.

ADR=adverse drug reaction; CSF=cerebrospinal fluid; DIAM=drug-induced aseptic meningitis; FcRn=neonatal Fc receptor; gMG=generalized myasthenia gravis; IgA=immunoglobulin A; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; MG=myasthenia gravis; [redacted]; SmPC=Summary of product characteristics.
Data sources: Summary of Clinical Safety (2.7.4); MG0007 CSR, Section 8.9.6.

Important potential risks

Important potential risks with rozanolixizumab treatment are characterized in the table below.

Table Part II–12: Important potential risk: Serious infections

Potential mechanisms	Rozanolixizumab is a humanized anti-FcRn monoclonal antibody that by blocking activity of FcRn accelerates the catabolism of IgG antibodies, including IgG autoantibodies. IgGs play an important role in protection against infections. Rozanolixizumab causes transient reduction in IgG and therefore has the theoretical potential to increase susceptibility to infections. However, considering that the levels of other immunoglobulin isotypes (eg, IgM, IgA) are unchanged, and that T-and B-cells function remains intact (thereby preserving the capacity to raise an immune response), the risk of infections is considered low.
Evidence source(s) and strength of evidence	This important potential risk is based on rozanolixizumab mechanism of action. Data to evaluate safety concerns derive from clinical studies.
Characterization of the risk	**Frequency:** In MG0003, there were no serious TEAEs of infections in any rozanolixizumab dose groups. In total, 31 (23.3%) rozanolixizumab-treated participants (10 [15.6%] in ≈7mg/kg and 21 [30.4%] in ≈10mg/kg) and 13 (19.4%) placebo-treated participants reported TEAEs of infections. The most frequently reported infections were nasopharyngitis (5 [7.2%]) in ≈10mg/kg, followed by placebo (3 [4.5%]) and ≈7mg/kg (1 [1.6%]); oral herpes, reported only in ≈10mg/kg (3 [4.3%]); and upper respiratory tract infection (2 [3.1%]) in ≈7mg/kg, followed by placebo (1 [1.5%]) and ≈10mg/kg (1 [1.4%]). In Pool S2, in total, 85 (45.2%) study participants experienced a TEAE within the SOC Infections and infestations, including 43 (32.3%) in the rozanolixizumab ≈7mg/kg and 54 (41.2%) in the ≈10mg/kg. The incidence of infections, including serious infections, did not increase with repeated cyclic treatment in any dose. The most common infections were COVID-19, upper respiratory tract infection, nasopharyngitis, and oral herpes. Discontinuations from the study and/or IMP due to infection occurred in <5% of participants ([1 (0.8%] in ≈7mg/kg and 5 [3.8%] in ≈10mg/kg). Serious infections occurred in 8 (4.3%) participants (2 [1.5%] in ≈7mg/kg and 6 [4.6%] in ≈10mg/kg [this includes 1 SAE of aseptic meningitis which was severe and led to discontinuation]). The most common serious infection was COVID-19 (3 [1.6%] of participants). In Pool S1, the types of TEAEs occurring in the SOC Infections and Infestations were similar to those occurring in Pool S2. There were no opportunistic infections reported in MG0003 or safety pools S2 and S1. In the completed OLE MG0007 study, a total of 90 (57.3%) rozanolixizumab-treated participants reported infections (47 [46.1%] and 59 [57.8%] in ≈7mg/kg group and ≈10mg/kg group, respectively). The incidence of infections was consistently below 30% in each cycle. The most common TEAEs (>10%) were

Table Part II–12: Important potential risk: Serious infections

	COVID-19, nasopharyngitis, and upper respiratory tract infections. Infections in 10 (6.4%) of participants (3 [2.9%] in ≈7mg/kg and 7 [6.9%] in ≈10mg/kg) led to permanent IMP discontinuation. Twelve (7.65%) study participants reported serious infections and the incidence of serious infections did not increase with repeated cyclic treatment. Four study participants reported infections which met criteria for opportunistic infections: 3 (2.9%) in the rozanolixizumab ≈7mg/kg group (sinusitis aspergillus, blastocystis infection, and ophthalmic herpes simplex) and 1 (1.0%) in the ≈10mg/kg group (oesophageal candidiasis). A medical review of these cases did not identify a concern for an increased risk of opportunistic infections associated with rozanolixizumab treatment (see details in MG0007 CSR Section 8.9.8). **Severity:** In MG0003, there were no infections of severe intensity reported with rozanolixizumab. In Pool S2, 7 (3.7%) participants had severe infections (1 [0.8%] in ≈7mg/kg and 6 [4.6%] in≈10mg/kg). The most common severe TEAE was COVID-19 (2 [1.1%] participants, both in ≈10mg/kg). In MG0007, incidence of severe infections was low: 11 (7.0%) participants reported severe infections (3 [2.9%] in ≈7mg/kg and 8 [7.8%] in ≈10mg/kg). The most common severe TEAE was COVID-19 infection. **Reversibility:** In MG0003, most of the TEAEs of infections (all nonserious) resolved while treatment with rozanolixizumab was continued, and no recurrent infections were observed with rozanolixizumab. No infections with fatal outcome were reported in MG0003. In Pool S2 of the 8 participants with serious TEAEs, 3 participants had fatal outcomes (2 participants in ≈10mg/kg with fatal COVID-19 and COVID-19 pneumonia; 1 participant in ≈7mg/kg with Pneumonia) and 5 participants (with 6 events) fully recovered from the event. In MG0007, most of the infections resolved during the study. Of the 12 participants with serious infection TEAEs, most recovered. Three TEAEs of infections had a fatal outcome: 1 event of COVID-19 and 1 event of COVID-19 pneumonia in the rozanolixizumab ≈10mg/kg group, and 1 event of pneumonia in the ≈7mg/kg group). None of the events were considered related to rozanolixizumab. One study participant (in the ≈10mg/kg group) who died due to cardiac failure had a background infection. There was no increase in serious infections with repeated cyclic treatment. **Post marketing data**: Based on the review of global post marketing data until 25 Dec 2023, no change in the characterization of this important potential risk is proposed.
	Long term outcome/ impact on quality of life: Serious infections may require medical intervention to be treated, including hospitalization. In a study conducted in Finland between Jan 2004 and Dec 2014, including all public health care hospital discharges from neurological, medical, surgical and intensive care units

Table Part II–12: Important potential risk: Serious infections

	in MG (n=2989), an infection was the primary diagnosis in 8% of admissions and this proportion increased from 5% to 10% during the study period. These admissions lasted longer than admissions with a non-infectious primary diagnosis (median 6, IQR 5 vs. median 4, IQR 4 days) and infection was associated with an increased risk of in-hospital mortality (HR of 6.9, 95% CI 3.3-14.5) (Sipila et al, 2019). No long-term effect is expected after resolution of a serious infection.
Absolute risk	Kassardjian et al (2020) used linked health administrative data and included 3,823 patients with MG and 15,292 comparators from the general population, matched for age, sex and region of residence. Over a mean of 5.4 (SD 3.8) years, a 39% increased risk of severe infection (ie, primary diagnosis on hospital or emergency records) was found for MG (72.5 vs 35.0 per 1000 person-years; AHR of 1.39, 95% CI 1.28-1.51). The most common types of infections diagnosed in patients with MG were all-cause respiratory infections (21.6%), bacterial pneumonia (15.8%), skin/soft tissue infections (9.6%) and septicemia (6.7%). Cases of meningitis, encephalitis, tuberculosis, candidiasis, aspergillosis and Pneumocystis jiroveci pneumonia were low (<6 cases each). A second study compared the incidence of tuberculosis between 2317 patients with MG and 23,170 age-, sex- and comorbidity-matched controls (Ou et al, 2013). The study period was between 2000 and 2006 and the median follow-up over 3 years. Incidence of tuberculosis was higher in MG than in the comparator group (29.2 vs. 1.3 per 10,000 person-years; AHR of 1.96, 95% CI 1.22-3.16) and most patients had pulmonary tuberculosis. In a third study, 861 patients with MG had a total of 2989 hospital admissions and the proportion of infections as the primary diagnosis increased from 4.5% to 10.4% during the study period. The most common diagnoses were lower respiratory tract infections (N=65/240, 27.1%), septicemia (N=36/240, 15%) and urinary tract infections (N=18/240, 7.5%) (Sipila et al, 2019).
Risk factors and risk groups	Muscle weakness, autoimmune disease mechanism and immunosuppressive treatment are the risk factors for infection in people with MG (Gilhus et al, 2018). Thymus disorder or thymectomy could also predispose to infections or to infection severity. Rurality, COPD, hypertension, prior infection, frailty and comorbidity burden have been deemed as risk factors for infection amongst patients with MG (Kassardjian et al, 2020).
Preventability	Treatment with rozanolixizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. During treatment with rozanolixizumab, monitor for clinical signs and symptoms of infections. If a clinically important active infection occurs, consider withholding rozanolixizumab until the infection has resolved (SmPC Section 4.4).
Impact on risk-benefit balance of the product	The vast majority of infections reported by the patients treated with rozanolixizumab were nonserious, mild to moderate, and did not lead to permanent study discontinuation. In MG0003 and Pool S2, the most common TEAEs were minor infections commonly occurring in the general population; eg,

Table Part II–12: Important potential risk: Serious infections

	upper respiratory tract infection, nasopharyngitis, and oral herpes. There was no increase in the incidence of infections with repeated cyclic treatment. There were no opportunistic infections reported in MG0003 or safety pools. Routine pharmacovigilance activities will be implemented to monitor this risk (see Part III). Risk of infection is included in the warnings and precautions for use (SmPC Section 4.4). Risk minimization activities are discussed in Part V.
Public health impact	No significant public health impact is expected. Per real world evidence data, MG is found to be independently associated with an increased risk of severe infection.

AHR=average hazard ratio; CI=confidence interval; COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019; FcRN=neonatal Fc receptor; HR=hazard ratio; Ig=immunoglobulin; IMP=investigational medicinal product; IQR= interquartile range; MG=myasthenia gravis; OLE=open label extension; PT=preferred term; SAE=serious adverse event; SD=standard deviation; SOC=System Organ Class; TEAE=treatment emergent adverse event.
Data sources: Summary of Clinical Safety (2.7.4); MG0003 CSR, Section 11.2.4, Table 9.1.3, Table 9.1.4; MG0007 CSR, Section 8.9.7 and 8.9.8.

SVII.3.2 Presentation of the missing information

Use during pregnancy

Evidence source:

Limited data does not allow to draw conclusion on the use of rozanolixizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As expected by the pharmacological mode of action of rozanolixizumab, offspring from treated dams had very low levels of IgG that normalized within 2 months.

Population in need of further characterization:

The safety and efficacy of rozanolixizumab use during pregnancy is not established.

Long-term safety

Evidence source:

Limited data are available on long-term use of rozanolixizumab in adult patients with gMG.

In MG0007, a Phase 3, multicenter, 2-arm, open label extension (OLE) study to evaluate 6-week treatment cycles of rozanolixizumab in study participants with gMG, the median (range) number of treatment cycles was 6.0 (1 to 17) with a median time in study of 24.20 months. A total of 125 study participants were in the study for ≥1 year and 80 study participants were in the study for ≥2 years.

The acceptable safety profile and tolerability of rozanolixizumab have been confirmed over long-term cyclic treatment in gMG patients. No new safety risks or changes to known safety risks were identified.

In summary, the results of this completed long-term OLE study confirm those results from the pivotal trial MG0003 and show that rozanolixizumab as an add-on to standard therapy provides

consistent long-term clinical benefit with an acceptable safety profile and tolerability in patients with gMG across long-term repeated cyclic treatment.

The available evidence in gMG and other indications is not suggestive for a different safety profile compared to short term use.

Population in need of further characterization:

Patients under long-term treatment with rozanolixizumab.

Part II Module SVIII Summary of the safety concerns

Table Part II–13: 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

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- A specific adverse reaction follow-up questionnaire form for suspected reports of DIAM will be utilized in the postmarketing setting. As DIAM is a diagnosis of exclusion and there is also an important potential risk of serious infections, the questionnaire will cover all forms of meningitis.

  This structured follow-up form is designed to optimize documentation of case reports of (aseptic) meningitis by means of collecting detailed information in a structured and standardized manner.

  The proposed questionnaire aims to collect information on the patient, exposure to rozanolixizumab and other drugs (such as nonsteroidal anti-inflammatory drugs, antibiotics, IVIg, mAb, and other FcRn blockers inhibitors), clinical presentation and diagnostic investigations, relevant medical history and risk factors of meningitis, including DIAM, treatment, and outcome of the event.

  The proposed follow-up questionnaire form is provided in EU RMP Part VII.

- Other forms of routine pharmacovigilance activities: None.

III.2 Additional pharmacovigilance activities

III.2.1 Rozanolixizumab observational secondary data study

Post-authorization safety study short name and title:

A multi-national cohort study to evaluate the safety of rozanolixizumab in patients with generalized myasthenia gravis (MG0027).

Rationale and study objectives:

The aim of this study is to investigate the long-term safety of rozanolixizumab. Serious infections and serious opportunistic infections will be described and patients with gMG exposed to rozanolixizumab and exposed to other gMG treatments (not exposed to rozanolixizumab) will be compared. A safety outcome with low incidence during the clinical development such as nonbacterial meningitis (as a proxy for drug induced aseptic meningitis), will also be assessed. Generalized myasthenia gravis treatment usage in real-world settings and the safety profile of rozanolixizumab used during pregnancy will be described.

Study design:

Retrospective observational study using secondary data of new users of rozanolixizumab with a comparison group of treated patients with gMG not treated with rozanolixizumab. The study will have a 6–8-year study period with an observation period of 3 years following first administration.

Study population:

New users of rozanolixizumab from the source population with MG during the study period; and a suitable comparator cohort of users of standard of care (ie, users of a list of pre-specified drugs) for MG, propensity score matched to rozanolixizumab users.

Milestones:

Protocol first submission: 05 Jul 2024

Progress report submission: Jun 2027

Interim reports submission: Jun 2029 and Jun 2032

Final reports submission: 31 Dec 2034

For further details please see EU RMP Part VII **Error! Reference source not found.** for the detailed synopsis.

III.3 Summary Table of additional Pharmacovigilance activities

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table Part III–1.

Table Part III–1: 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	05 Jul 2024
			Interim report submissions	Jun 2027 (progress report) Jun 2029 (interim report 1) Jun 2032 (interim report 2)
			Final report submission	31 Dec 2034

DIAM=drug-induced aseptic meningitis; gMG=generalized myasthenia gravis; MA=marketing authorization; MG=myasthenia gravis.

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for rozanolixizumab.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 Routine Risk Minimization Measures

Description of routine risk minimization measures by safety concern is presented in Table Part V–1.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Aseptic Meningitis (DIAM)	**Routine risk communication:** The risk of aseptic meningitis (DIAM) is discussed in SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects) and PL Section 2 (What you need to know before you use Rystiggo). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special warnings and precautions for use): Recommendation for monitoring for signs of aseptic meningitis and performing diagnostic workup and treatment. PL Section 2 (What you need to know before you use Rystiggo): Recommendation to inform the doctor of any signs or symptoms of aseptic meningitis. **Other routine risk minimization measure beyond the Product Information:** 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.
Important potential risks	
Serious infections	**Routine risk communication:** The risk of infections is discussed in SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (What you need to know before you use Rystiggo). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special warnings and precautions for use): Recommendation for monitoring of infections and measures related to infections.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
	PL Section 2 (What you need to know before you use Rystiggo): Recommendation to inform the doctor of any infections before starting or during treatment with rozanolixizumab. **Other routine risk minimization measure beyond the Product Information:** 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.
Missing information	
Use during pregnancy	**Routine risk communication:** SmPC Section 4.6 (Fertility, pregnancy, and lactation). PL Section 2 (What you need to know before you use Rystiggo). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 (Fertility, pregnancy, and lactation). PL Section 2 (What you need to know before you use Rystiggo). **Other routine risk minimization measure beyond the Product Information:** 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.
Long-term safety	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measure beyond the Product Information:** 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.

DIAM=drug-induced aseptic meningitis; NA=not applicable; PL=package leaflet; SmPC=summary of product characteristics

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Section V.1 are sufficient to manage the safety concerns of rozanolixizumab. Additional risk minimization measures are not considered necessary.

V.3 Summary of risk minimization measures

Table Part V–2 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table Part V–2: Table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Aseptic meningitis (DIAM)	**Routine risk minimization 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) SmPC Section 4.8 (Undesirable effects) 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 utilized in the postmarketing setting. **Additional PhV activities:** Real-world rozanolixizumab safety study using secondary data (PASS MG0027).
Important potential risks		
Serious infections	**Routine risk minimization 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). **Additional risk minimization 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).

Table Part V–2: Table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Missing information		
Use during pregnancy	**Routine risk minimization 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 minimization 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 minimization 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 minimization 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).

DIAM=drug-induced aseptic meningitis; NA=not applicable; PASS=post-authorization safety study; PhV=pharmacovigilance; PL=package leaflet; SmPC=summary of product characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR RYSTIGGO (ROZANOLIXIZUMAB)

This is a summary of the risk management plan (RMP) for Rystiggo. The RMP details important risks of Rystiggo, how these risks can be minimized, and how more information will be obtained about Rystiggo's risks and uncertainties (missing information).

Rystiggo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rystiggo should be used.

This summary of the RMP for Rystiggo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rystiggo's RMP.

I The medicine and what it is used for

Rystiggo is authorized as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor or anti-muscle specific kinase antibody positive (see SmPC Section 4.1 for the full indication). Rystiggo contains rozanolixizumab as the active substance and it is given subcutaneously via infusion.

Further information about the evaluation of Rystiggo’s benefits can be found in Rystiggo’s EPAR, including in its plain-language summary, available on the European Medicine Agency (EMA) website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/rystiggo.

II Risks associated with the medicine and activities to minimize or further characterise the risks

Important risks of Rystiggo, together with measures to minimize such risks and the proposed studies for learning more about Rystiggo 's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Rystiggo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rystiggo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rystiggo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

List of important risks and missing information	
Important identified risks	Aseptic meningitis (drug-induced aseptic meningitis)
Important potential risks	Serious infections
Missing information	Use during pregnancy Long-term safety

II.B Summary of important risks

Summary of important risks

Important identified risks: aseptic meningitis (DIAM)	
Evidence for linking the risk to the medicine	Aseptic meningitis (DIAM) has been reported following rozanolixizumab treatment with subsequent recovery without sequelae. The mechanism of aseptic meningitis (DIAM) with rozanolixizumab is unknown.
Risk factors and risk groups	Patients with chronic migraine are at higher risk of developing DIAM, given the experience seen with IVIg (Yelehe-Okouma et al, 2018, Sekul et al, 1994).
Risk minimization measures	Routine risk minimization measures: – SmPC Section 4.2 (Posology and method of administration) – SmPC Section 4.4 (Special warnings and precautions for use) – SmPC Section 4.8 (Undesirable effects) – PL Section 2 (What you need to know before you use Rystiggo)

Summary of important risks

	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): Recommendation for monitoring for signs of aseptic meningitis and performing diagnostic workup and treatment. PL Section 2 (What you need to know before you use Rystiggo): Recommendation to inform the doctor of any signs or symptoms of aseptic meningitis. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Real-world rozanolixizumab safety study using secondary data (PASS MG0027) See Section II.C of this summary for an overview of the postauthorization development plan.
Important potential risks: serious infections	
Evidence for linking the risk to the medicine	Rozanolixizumab blocks the activity of FcRn and accelerates the catabolism of IgG antibodies, leading to a transient decrease of IgG levels, which may increase the risk of infections. Rozanolixizumab has no impact on other immunoglobulin isotypes (eg, IgM, IgA) or on the function of T-and B-cells. Following repeated cyclic treatment in Phase III studies in gMG, infections were reported in 45.2% of patients treated with rozanolixizumab and no increase in the incidence of infections was observed with each subsequent cycle. Most infections reported by the patients treated with rozanolixizumab were nonserious, mild to moderate, and did not lead to permanent study discontinuation. Serious infections were reported in 4.3% of patients treated with rozanolixizumab. There were no opportunistic infections reported in MG0003 or safety pools S2 and S1.
Risk factors and risk groups	Muscle weakness, autoimmune disease mechanism and immunosuppressive treatment are the risk factors for infection in people with MG (Gilhus et al, 2018). Thymus disorder or thymectomy could also predispose to infections or to infection severity. Rurality, COPD, hypertension, prior infection, frailty and comorbidity burden have been deemed as risk factors for infection amongst patients with MG (Kassardjian et al, 2020).
Risk minimization measures	Routine risk minimization measures: – SmPC Section 4.2 (Posology and method of administration) – SmPC Section 4.4 (Special warnings and precautions for use) – PL Section 2 (What you need to know before you use Rystiggo) SmPC Section 4.2 (Posology and method of administration): Treatment should be initiated and supervised by specialist healthcare professionals experienced

Summary of important risks

	in the management of patients with neuromuscular or neuro-inflammatory disorders. SmPC Section 4.4 (Special warnings and precautions for use): Recommendation for monitoring of infections and measures related to infections. PL Section 2 (What you need to know before you use Rystiggo): Recommendation to inform the doctor of any infections before starting or during treatment with rozanolixizumab. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Real-world rozanolixizumab safety study using secondary data (PASS MG0027) See Section II.C of this summary for an overview of the postauthorization development plan.
Missing information: Use during pregnancy	
Risk minimization measures	Routine risk minimization measures: – SmPC Section 4.2 (Posology and method of administration) – SmPC Section 4.6 (Fertility, pregnancy, and lactation) – PL Section 2 (What you need to know before you use Rystiggo) 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 minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Real-world rozanolixizumab safety study using secondary data (PASS MG0027) See Section II.C of this summary for an overview of the postauthorization development plan.
Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization 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 minimization measures: None

Summary of important risks

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Real-world rozanolixizumab safety study using secondary data (PASS MG0027) See Section II.C of this summary for an overview of the postauthorization plan.

COPD=chronic obstructive pulmonary disease; DIAM=drug-induced aseptic meningitis; Ig=immunoglobulin; MG=myasthenia gravis; PASS=post-authorization safety study; PL=package leaflet; SmPC=summary of product characteristics

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Rystiggo.

II.C.2 Other studies in post-authorization development plan

Additional pharmacovigilance activities include the following studies:

Real-world rozanolixizumab safety study using secondary data in patients with MG (MG0027)

Study short name: Real-world rozanolixizumab safety study using secondary data in patients with myasthenia gravis (MG) (MG0027).

Purpose of the study: The aim of this study is to investigate the long-term safety of rozanolixizumab. Serious infections and serious opportunistic infections will be described and gMG patients exposed to rozanolixizumab and exposed to other gMG treatments (not exposed to rozanolixizumab) will be compared. A safety outcome with low incidence during the clinical development such as nonbacterial meningitis (as a proxy for drug induced aseptic meningitis), will also be assessed. Generalized myasthenia gravis treatment usage in real-world settings and the safety profile of rozanolixizumab used during pregnancy will be described.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

A specific adverse reaction follow-up questionnaire form for (aseptic) meningitis will be utilized in the postmarketing setting. As DIAM is a diagnosis of exclusion and there is also an important potential risk of serious infections, the questionnaire will cover all forms of meningitis. The follow-up questionnaire form is included below.

UCB Global DS database #: Click or tap here to enter text.**UCB LAM ID #:** Click or tap here to enter text.

For completion by UCB Patient Safety

Diagnosis *(including presumptive and differential)*: Click or tap here to enter text.

Patient Information

Height: Click or tap here to enter text.**Ft & In or Meters:** Choose an item.

Weight: Click or tap here to enter text.**Lbs or Kg:** Choose an item.

Clinical symptoms

Which of the following best describes how the patient is affected overall?Choose an item.

☐Headache
☐Fever; Temperature: Click or tap here to enter text. °C/°F: Choose an item.
☐Nausea
☐Vomiting
☐Diarrhoea
☐Increased sensitivity to light
☐Neck stiffness
☐Neck pain
☐Dizziness
☐Dizziness with vertigo
☐Rash; Please describe: Click or tap here to enter text.
☐Arthralgia
☐Myalgia
☐Increased sensitivity to noise
☐Increased sensitivity to smell
☐Headache made worse by routine physical activity
☐Weakness on one side
☐Seeing shimmering lights, lines, dark spots, other shapes, or colors before the eyes, before or during a headache and lasting more than a few minutes but less than an hour
☐One-sided numbness of lips, tongue, fingers, or legs that migrates or moves and starts before the headache becomes severe and lasts less than an hour
☐Confusion/altered mental status
☐Other, please specify: Click or tap here to enter text.

What was the time interval from the last dose of Rystiggo to start of symptoms?Click or tap here to enter text.

Was this the first dose of Rystiggo? Choose an item.

Is the patient taking any other drugs? Choose an item.

If so, please list the drug(s) and their indication(s) if known: Click or tap here to enter text.

Were any of these drugs recently started ie in the last 3 months? Choose an item.

If yes, please specify the drug(s) and the approximate start date: Click or tap here to enter text.

Diagnostic tests and date collected

☐Lumbar puncture Click or tap to enter a date.

☐PCR Click or tap to enter a date.

☐Cultures Click or tap to enter a date.

☐Brain scan without gadolinium Click or tap to enter a date.

☐Brain scan with gadolinium Click or tap to enter a date.

☐Other: Click or tap here to enter text.. Click or tap to enter a date.

Test Results

Cerebrospinal Fluid (CSF) Profile

Appearance: Click or tap here to enter text.

Pressure (cm H20): Click or tap here to enter text.

Glucose (mg/dL/mmol/L): Click or tap here to enter text. **;** Click or tap to enter a date.

Protein (mg/dL/mmol/L): Click or tap here to enter text. **;** Click or tap to enter a date.

Red Blood Cells (µL/mm^3): Click or tap here to enter text. **;** Click or tap to enter a date.

White Blood Cells (µL /mm^3): Click or tap here to enter text. **;** Click or tap to enter a date.

Other: Click or tap here to enter text.

Imaging: Click or tap here to enter text.

Risk Factors

☐Migraine

If yes, please specify frequency, and duration : Click or tap here to enter text.

☐Headaches other than migraine requiring regular medication

If yes, please specify frequency, and duration: Click or tap here to enter text.

☐Aseptic meningitis

If yes, was there a cause identified? If so, please specify: Click or tap here to enter text.

☐Drug-induced aseptic meningitis:

If yes, please specify drug, duration of exposure prior to event and max intensity, if known:

Click or tap here to enter text.

☐Other types of meningitis

If yes, please specify: Click or tap here to enter text.

☐Previous medical history of Immunoglobulin (IG) administration

If yes, were there any episodes of aseptic meningitis associated during/after the IG administration: Choose an item.

If yes, duration of exposure prior to event (if known): Click or tap here to enter text.

☐Other: Click or tap here to enter text.

Event treatment

Please specify the therapeutic measures taken due to the event:

☐Medications: Click or tap here to enter text.

☐Other: Click or tap here to enter text.

What was the outcome of the event?: Choose an item.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.