CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761286Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761286
PDUFA Goal Date	June 24, 2023
OSE RCM #	2022-2502
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 22, 2023
Subject	Evaluation of Need for a REMS
Established Name	Rozanolixizumab-noli
Trade Name	Rystiggo
Name of Applicant	UCB, Inc.
Therapeutic Class	Neonatal fragment crystallizable receptor blocker
Formulation(s)	280 mg/2 mL injection for subcutaneous infusion
Dosing Regimen	420 mg (patients (b) (4) <50 kg) or 560 mg (patients (b) (4) kg) infused once weekly for 6 weeks

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rystiggo (rozanolixizumab) is necessary to ensure the benefits outweigh its risks. UCB, Inc. submitted a Biologic Licensing Application (BLA) 761286 for rozanolixizumab with the proposed indication for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive. This application is under review in the Division of Neurology 1 (DN1). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rystiggo (rozanolixizumab), a new molecular entity[a], is a recombinant, humanized anti-neonatal Fc receptor (FcRn) blocker of the immunoglobin G (IgG) 4 isotype and is proposed for treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor or anti-muscle-specific tyrosine kinase antibody positive. Rozanolixizumab decreases serum IgG concentration by inhibiting the binding of IgG to (FcRn), a receptor that normally protects IgG from intracellular degradation and recycles IgG back to the cell. By this mechanism, rozanolixizumab decreases the concentration of pathogenic IgG autoantibodies associated with gMG. The proposed formulation for rozanolixizumab is a 280 mg/2mL single-dose vial to be administered as a subcutaneous infusion once weekly for 6 weeks.[b] Subsequent treatment cycles are to be administered based on clinical evaluation. The recommended dosage is 420 mg for patients (b) (4) <50 kg and 560 mg for patients (b) (4). It is anticipated that rozanolixizumab will be administered in both the outpatient and inpatient settings for chronic therapy.[c] Rozanolixizumab was granted orphan drug designation on February 1, 2019 under the investigational new drug (IND) application 132407. Priority review for rozanolixizumab, BLA 761286, was granted December 21, 2022. Rozanolixizumab is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761286 relevant to this review:

- 02/01/2019: Orphan drug designation granted for rozanolixizumab under IND 132407.
- 10/24/2022: Rozanolixizumab, BLA 761286 submission for the treatment of gMG in adult patients who are AChR or MuSK antibody positive.
- 12/21/2022: Priority Review granted for Rozanolixizumab, BLA 761286.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor *(D): The expected or actual duration of treatment with the drug*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Myasthenia gravis (MG) is a rare chronic autoimmune, neuromuscular disease characterized by weakness and fatigability of skeletal muscles. The disease is caused by a defect in the action of acetylcholine at neuromuscular junctions and is often associated with thymic follicular hyperplasia or thymoma. Onset of the disease may be sudden with variable severity in symptoms which often include ocular, bulbar, limb and respiratory muscles. Weakness and fatigue of these muscles can cause problems with eating and drinking and ultimately lead to life-threatening difficulties with breathing and swallowing.[d]

The prevalence of MG in the United States is estimated at 14 to 20 cases per 100,000 people.[1e] It most commonly impacts young adult females (under 40) and older males (over 60), but can occur at any age, including childhood. There is no cure for MG, but as many as 40% of patients achieve complete remission. Approximately 3-4% of individuals with MG die from the condition.[2]

3.2. Description of Current Treatment Options

In general, the approach to MG therapy typically involves symptomatic treatment, chronic immunotherapies, immunomodulating treatments and thymectomy surgery. There are four products with FDA approval for the treatment of generalized MG.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Summary of FDA-approved Treatment Options for Generalized Myasthenia Gravis:

Product Trade Name (Generic) Year of gMG Indication Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Ultomiris® (ravulizumab) 2022	gMG in adult patients who are anti-AChR antibody-positive	300 mg/30 mL and 1,100 mg/11 mL solution for IV injection- weight based dosing	Meningococcal vaccination recommended, Infusion-related reactions	REMS for serious meningococcal infections, Boxed Warning, MG
Vyvgart™ (efgartigimod) 2021	gMG in patients who are anti-AChR antibody positive	400 mg/20 mL solution for IV injection- weight based dosing	Serious infections, Hypersensitivity	Labeled Warnings & Precautions
Soliris® (eculizumab) 2017	gMG in patients who are anti-AChR antibody positive	300 mg/30 mL solution for IV injection- weight based dosing	Meningococcal vaccination recommended, Infusion-related reactions	REMS for serious meningococcal infections, Boxed Warning, MG
Mestinon® (pyridostigmine) 1955	MG	60 mg tablets, 180 mg CR tablets, 60 mg/5 mL syrup, 5 mg/mL solution for IV injection- dosing is typically 600 mg per day	Cholinergic crisis	Labeled warning

Symptomatic Treatment: For symptomatic treatment in patients with mild to moderate MG, an acetylcholinesterase inhibitor, such as pyridostigmine, is used to increase the amount of acetylcholine available in the neuromuscular junction, thereby improving signal transmission. Patients' response to acetylcholinesterase inhibitors is variable and reduced dosing may be needed to minimize cholinergic side effects and prevent cholinergic crisis.

Chronic Immunotherapies: Patients whose symptoms are not significantly resolved with acetylcholinesterase inhibitors often begin immunotherapy with a glucocorticoid, such as prednisone. Chronic, high-dose, oral prednisone has been used to treat MG for decades, however, significant adverse effects from long term steroid therapy (hypertension, glucose intolerance, peripheral edema, psychiatric changes, etc.) has led providers to consider limitations on their use.[3] Non-steroidal immunotherapeutic agents provide another treatment option for patients who are not responding to or are experiencing adverse effects from glucocorticoids. Efgartigimod, ultomiris and eculizumab are immunotherapies that are FDA approved to treat gMG. Ultomiris and eculizumab are approved with REMS to mitigate the risk of serious meningococcal infections. The drugs azathioprine and mycophenolate are other options for non-steroidal therapies for MG treatment.[4] Both drugs are used to reduce the autoimmune reactivity associated with MG, and each carries serious risks with treatment. Azathioprine has a boxed warning for malignancy and has also been associated with cytopenias, serious infections and teratogenicity. Mycophenolate is also a teratogen and has a boxed warning and approved with a REMS to mitigate the risk of embryofetal toxicity. Other serious mycophenolate risks included in the boxed warning are malignancies and serious infections. In addition to azathioprine and mycophenolate, there are a number of other chronic immunotherapies that have been used to treat MG, such as cyclosporine, tacrolimus and methotrexate. These drugs have been used with varying benefit and the serious side effects associated with them often limit their usage. Nephrotoxicity, malignancies and embryofetal toxicity have been associated with their use.

Immunomodulating Treatments: Plasmapheresis and intravenous immunoglobulin (IVIG) are considered for MG patients whose condition is still deteriorating despite having exhausted other therapies. These treatments are limited by their restriction to major medical institutions and have led to serious adverse events of hypotension and arrythmias (plasmapheresis), as well as renal failure and thrombolytic events (IVIG).[5]

Thymectomy: In a minority of patients with MG, a thymic epithelial tumor (thymoma) led to their condition.[6] Surgical removal of the thymus gland is indicated for these patients and is also recommended for patients under 60 years of age who have mild to moderate muscle weakness from MG.[7] Adverse events that may occur related to a thymectomy include MG crisis, infections and nerve injury.[8]

Although there are several treatments approved to treat patients with gMG, there remains a need for effective treatments because not all MG patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments.

4. Benefit Assessment

The pivotal study used to establish efficacy of rozanolixizumab was a single randomized, double-blind, placebo-controlled Phase 3 study (MG0003 [NCT03971422]) evaluating two doses of rozanolixizumab and matching placebo in adult patients with gMG experiencing moderate to severe symptoms and being considered for additional treatment such as intravenous immunoglobulin (IVIg) or plasma exchange (PEX). In study MG003 a total of 200 subjects were randomized to receive six SC infusions of

rozanolixizumab at ≈7mg/kg (N=66) or ≈10mg/kg (N=67) or matching placebo (N=67). Treatment consisted of one dose per week for six weeks followed by an observation period of up to eight weeks. The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL)[f] total score at day 43. The MG-ADL assesses the impact of gMG on daily functions of eight signs and symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale with higher scores indicating more impairment. At Day 43 of the study, the primary endpoint showed improvement from baseline that was statistically significantly different compared to placebo for both ≈7mg/kg and ≈10mg/kg rozanolixizumab treatment groups (p-value <0.001). The change from baseline in MG-ADL total score to Day 43 was approximately 2.6 points in favor of both rozanolixizumab treatment groups.

The secondary endpoint of MG-ADL responder rate at Day 43 was also met. A responder represented at least a 2-point improvement from baseline in the MG-ADL total score. The percentage of clinical responders at Day 43 were 68.2% (n=45) for the ≈7mg/kg rozanolixizumab group, 61.2% (n=41) for the ≈10mg/kg group and 28.4% (n=19) for the placebo group.

The clinical reviewer concluded that the applicant provided reliable and statistically persuasive evidence that rozanolixizumab can help patients with anti-AChR or anti-MuSK antibody positive gMG achieve a clinically meaningful improvement in the symptoms of the disease that affect their activities of daily living, motor function, and disease severity.[9]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis was evaluated based on data from the pivotal Phase 3 trial (MG003). Supportive data from the two open-label extension (OLE) studies (MG004 [NCT04124965], MG007 [NCT04650854]) is also provided. The total patient population for the primary safety analysis consists of 200 patients of which 133 received at least one dose of rozanolixizumab ≈7mg/kg or ≈10mg/kg.

No deaths were reported in the primary safety pool, however five were reported in the MG007 OLE study (N=165) as of the February 3, 2023 120-day safety update. Two deaths were attributed to severe acute respiratory syndrome coronavirus (COVID-19) pneumonia in unvaccinated individuals. One death was due to multilobar pneumonia in which no pathogen was identified. And two deaths were attributed to cardiac events that occurred during the follow-up period and before treatment in Study MG0007. Each of the patients received at least one dose of study drug. The applicant stated that the deaths were assessed as unrelated to rozanolixizumab treatment. The medical officer agrees that the cardiac deaths were unrelated to rozanolixizumab based on the time to onset and presence of medical comorbidities. She concluded that "a role for rozanolixizumab in the treatment emergent adverse events of COVID-19 and pneumonia cannot be ruled out".[10]

[f] The Myasthenia Gravis-Specific Activities of Daily Living scale assesses the impact of gMG on daily functions of 8 signs and symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where 0

The incidence of serious adverse events (SAE) in study MG003 was 5 (7.8%) in the ≈7mg/kg rozanolixizumab group, 7 (10.1%) in the ≈10mg/kg group and 6 (9.0%) in the placebo group. Table 1 lists the SAE that occurred.

TABLE 1: Serious adverse events, Safety Population, Study MG0003

SAE Preferred Term	Placebo N=67 n (%)	RLZ ~ 7mg/kg N=64 n (%)	RLZ ~ 10mg/kg N=69 n(%)	RLZ Total N=133 n (%)	RLZ Total vs Placebo Risk Difference (%) (95% CI)
Any SAE	6 (9 0)	5 (7 8)	7 (10.1)	12 (9.0)	0.1 (-8.3, 8.5)
Gastritis	0	1 (1 6)	0	1 (0.8)	0.8 (-0.7, 2.2)
Vomiting	0	1 (1 6)	0	1 (0.8)	0.8 (-0.7, 2.2)
Chest pain	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)
COVID-19 pneumonia	1 (1 5)	0	0	0	-1.5 (4.4, 1.4)
Seizure	0	1 (1 6)	0	1 (0.8)	0.8 (-0.7, 2.2)
Headache	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)
Myasthenia gravis	1 (1 5)	1 (1 6)	2 (2.9)	3 (2.3)	0.8 (-3.1, 4.6)
Myasthenia gravis crisis	2 (3 0)	0	0	0	-3.0 (-7.1, 1.1)
Acute respiratory failure	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)
Nephrolithiasis	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)
Muscle weakness	1 (1 5)	0	0	0	-1.5 (4.4, 1.4)
Arthralgia	0	1 (1 6)	0	1 (0.8)	0.8 (-0.7, 2.2)
Metastatic squamous cell carcinoma	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)
Cervical dysplasia	0	1 (1 6)	0	1 (0.8)	0.8 (-0.7, 2.2)
Thoracic vertebral fracture	1 (1 5)	0	0	0	-1.5 (4.4, 1.4)
Device dislocation[1]	0	0	1 (1.4)	1 (0.8)	0.8 (-0.7, 2.2)

[1]Unrelated to MG, attributed to tracheostomy device dislocation

Source:MankodiA, MD- 01.30.2023 Midcycle Meeting Slides

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The incidence rates were similar for the rozanolixizumab and placebo treatment groups.

5.1. Serious Infections

Serious infections, including aseptic meningitis, were reported in the rozanolixizumab clinical development program. A total of eight serious infections were identified. In the pivotal trial there was one COVID-19 pneumonia case in a patient treated with placebo but no serious infections reported in the study drug groups. The other seven serious infections were identified in rozanolixizumab patients in the long-term extension trials (MG004, MG007) and are included in Table 2.

Table 2: Serious Infections in Rozanolixizumab-treated Patients in Studies MG003, MG004, MG007

System Organ Class FMQ (Narrow) Preferred Term	Rozanolixizumab Total N=196 n (%)
Any infection	8 (4.1)
Viral Infection (FMQ)	
COVID-19	3 (1.5)
COVID-19 pneumonia	1 (0.5)
Bacterial Infection (FMQ)	
Complicated appendicitis	1 (0.5)
Urosepsis	1 (0.5)
Pneumonia (FMQ)	
Pneumonia	1 (0.5)
Purulent Material (FMQ)	
Liver abscess	1 (0.5)
"Aseptic meningitis"	1 (0.5)

Source: Mankodi A, BLA 761286 Internal Midcycle Meeting Slides

The proposed label for rozanolixizumab includes a Warning and Precaution for infections. It instructs providers to monitor for infection signs and symptoms and to consider delaying or withholding rozanolixizumab treatment until infections have resolved. The label also includes a separate Warning and Precaution for aseptic meningitis. There was one case reported in Study MG007, but two cases reported in the IND application associated with this BLA (IND (b) (4)). The patient in Study MG007 developed symptoms within two days of rozanolixizumab administration and was subsequently hospitalized. Her symptoms resolved without sequelae after discontinuation of study drug. Draft labeling includes a Warning and Precaution stating that serious events of aseptic meningitis have been reported and that the patient should be monitored for symptoms and treated according to standard of care. DN1 also intends to request enhanced pharmacovigilance for serious adverse events related to infections, reactivation of latent tuberculosis and hepatitis B.

5.2. Hypersensitivity Reactions

Hypersensitivity reactions were observed in patients treated with rozanolixizumab. In study MG003 hypersensitivity reactions were observed in 7 (10.9%) of the ≈7mg/kg treatment group and 4 (5.8%) of the ≈10mg/kg group compared to 1 (1.5%) in the placebo treated patients. Some of the reactions included rash, urticaria, erythema and swollen tongue, which were of mild to moderate intensity. None of the reactions led to permanent discontinuation of study drug. Draft labeling includes a

hypersensitivity reaction Warning and Precaution and instructs providers to discontinue the infusion and administer appropriate therapy if a reaction occurs.

The clinical reviewer concluded that the available safety data show that risks of rozanolixizumab are acceptable for its intended use. She stated that she concurs that the identified risks can be mitigated through labeling and further evaluated during routine and enhanced pharmacovigilance."[11]

6. Expected Postmarket Use

Rozanolixizumab will likely be prescribed by neurologists and other specialists who have experience treating MG and other neurological conditions. These prescribers should be knowledgeable about the risks of serious infections and hypersensitivity associated with products used to treat gMG. It is expected that rozanolixizumab will be administered in both the outpatient and inpatient setting by healthcare providers proficient with infusion preparation and administration. These providers can counsel patients at the point of care regarding the potential for hypersensitivity and serious infections. The gMG patient population will likely be able to recognize the symptoms associated with these adverse effects and take necessary actions to manage them.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for rozanolixizumab beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of rozanolixizumab for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor or anti-muscle-specific tyrosine kinase antibody positive.

Myasthenia gravis is a rare chronic autoimmune, neuromuscular disease characterized by weakness and fatigability of skeletal muscles and can lead to life-threatening difficulties with breathing and swallowing. The benefits of gMG treatment with rozanolixizumab were demonstrated by meeting the primary endpoint of a statistically significant ($p<0.001$) MG-ADL change from baseline to Day 43 in the Phase 3 Study MG003.

The safety profile for rozanolixizumab is similar to that of efgartigimod, also a Fc receptor-inhibitor, which was approved without a REMS in 2021 to treat gMG. Serious infections and hypersensitivity reactions were observed in both clinical trial programs. Draft labeling for rozanolixizumab includes warnings and precautions for serious infections, including aseptic meningitis, and hypersensitivity reactions. Also, DN1 will request enhanced pharmacovigilance for serious adverse events related to infections, reactivation of latent tuberculosis and hepatitis B.

The healthcare providers who are likely to prescribe rozanolixizumab should be familiar with immunomodulatory therapies to treat gMG and knowledgeable about the risks of serious infections and hypersensitivity that is common with them. Additionally, enhanced pharmacovigilance regarding

serious infections will assist with identifying these adverse events in the postmarket setting. Therefore, based on the data currently available, DRM and DN1 agree that a REMS is not necessary to ensure the benefits outweigh the risks of rozanolixizumab.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks for rozanolixizumab. In general, healthcare providers who treat MG are familiar with the risks of serious infections and hypersensitivity reactions that can occur with use of immunotherapies. These healthcare providers will likely be specialists and understand the importance of patient monitoring. At the time of this review, labeling is ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Pool JJ. The outlook for someone with myasthenia gravis. Myasthenia-Gravis.com February 8, 2021. Accessed February 16, 2023.

[2] Pool JJ. The outlook for someone with myasthenia gravis. Myasthenia-Gravis.com February 8, 2021. Accessed February 16, 2023.

[3] Kaminski HJ, Denk J. Corticosteroid Treatment-Resistance in Myasthenia Gravis. *Front Neurol.* 2022; 13: 886625.

[4] UpToDate Chronic immunotherapy for myasthenia gravis - UpToDate

[5] Jhangiani H, IVIG. *Ameripharma Specialty Care*, 2023.

[6] UpToDate. Role of thymectomy in patients with myasthenia gravis - UpToDate

[7] Aydin Y, Ulas AB, Mutlu V, Eroglu A. Thymectomy in Myasthenia Gravis. *Eurasian J Med*. 2017;491(1):48-52.

[8] Aydin Y, Ulas AB, Mutlu V, Eroglu A. Thymectomy in Myasthenia Gravis. *Eurasian J Med*. 2017;491(1):48-52.

[9] Mankodi A. Integrated Review for Rystiggo (rozanolixizumab), BLA 761286, June 21, 2023.

[10] Mankodi A. Integrated Review for Rystiggo (rozanolixizumab), BLA 761286, June 21, 2023.

[11] Mankodi A. Integrated Review for Rystiggo (rozanolixizumab), BLA 761286, June 21, 2023.

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/s/

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