Rozanolixizumab-noli (RYSTIGGO)
National Drug Monograph
November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Rozanolixizumab-noli is a neonatal Fc receptor blocker which in turn reduces immunoglobulin G (IgG).

Indication(s) Under Review in This Document

- People with generalized myasthenia gravis (gMG) who are positive for the acetylcholine receptor antibody (AChR+) or muscle-specific tyrosine kinase antibody (MuSK+).

Dosage Form(s) Under Review

- Single dose vial for injection 280mg/2mL administered via subcutaneous (SC) infusion.

Clinical Evidence Summary

Efficacy Considerations

Phase I trial

A small phase I trial in healthy human participants provides some insights to pharmacodynamic effects of rozanolixizumab on serum IgG concentrations.[1] Participants were randomized to rozanolixizumab 1, 4, or 7 mg/kg or placebo for 28 days. Half of the matched cohorts were administered rozanolixizumab or placebo via intravenous infusion and the other half were administered rozanolixizumab or placebo via SC infusion. Both methods of administration saw similar reductions in serum IgG with the greatest mean reduction occurring between days 7-10. After cessation of therapy, serum IgG levels returned to baseline by day 57 (29 days after treatment ended).

Phase II trial

A phase IIa randomized, double-blind, placebo-controlled trial was conducted in 43 patients with gMG in 2 periods. In period 1 (days 1-29), patients received three once-weekly SC infusions of rozanolixizumab 7 mg/kg or placebo. In period 2 (days 29-43), patients were re-randomized to receive once weekly SC infusions of either rozanolixizumab 7 mg/kg or 4 mg/kg (period 2 had no placebo group). An observational period followed for days 44-99 where patients did not receive any therapy. The primary outcome was the change in the Quantitative Myasthenia Gravis (QMG) score from baseline to day 29 (i.e. the end of period 1). Some secondary outcomes did include MG clinical

outcomes through the end of period. However, it should be noted, from the phase I trial described above, that if a patient was in the rozanolixizumab 7 mg/kg period 1 subgroup and rozanolixizumab 4 mg/kg period 2 subgroup, it is possible that residual IgG lowering effects of the period 1 dose were affecting outcomes seen in period 2.

Patients could be either acetylcholine receptor antibody positive (AChR+) or muscle-specific kinase antibody positive (MuSK+). However, of all 43 patients, only one was MuSK+. Despite the title of the article stating "moderate to severe" gMG, the vast majority of patients (93%) were almost evenly distributed between baseline Myasthenia Gravis Foundation of America (MGFA) disease class II or III which represents mild to moderate weakness. About half of all patients were on steroids (47%) and/or immunosuppressants (49%). Concurrent MG immunosuppressant therapy could not be antiCD20 antibodies, immunoglobulin therapy or plasma exchange. Efgartigimod and ravulizumab were not FDA approved at the time. Forty-nine percent of patients had a thymectomy prior to baseline. Almost all patients were on cholinesterase inhibitors (91%). The primary endpoint failed to reach statistical significance with a QMG score least squares mean of rozanolixizumab versus placebo being -1.8 vs. -1.2 (p=0.221). Overall, rozanolixizumab had higher responder rates (3 or more point improvement on QMG) than placebo. It should be noted that a 3 or more point difference is considered clinically meaningful.[3] On day 22, rozanolixizumab had its peak responder rate, as 52% of patients had a clinically meaningful improvement in QMG score. In period 2, patients who remained on rozanolixizumab 7 mg/kg had the best QMG improvement from baseline, followed by those switched from placebo to rozanolixizumab 7 mg/kg. Patients who were switched from either placebo or rozanolixizumab 7 mg/kg to rozanolixizumab 4 mg/kg had the smallest change from baseline QMG score. This represents a dose dependent effect of this drug.

Phase III (MycarinG)

The pivotal trial for rozanolixizumab was a randomized, double-blind, placebo-controlled study of 200 patients randomized 1:1:1 to rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo via weekly SC infusions for 6 weeks.[4] Similar to the phase II trial, typical MG oral immunosuppressant and steroid therapy were allowed, but biologics, immunoglobulins, etc. were not. After the intervention period, there was an observational period of 8 weeks with no treatment. The primary efficacy endpoint was the change in Myasthenia Gravis Activities of Daily Living (MG-ADL) score from baseline to day 43. Note this is a different rating scale than the phase II study's primary outcome. QMG is a physician-assessed metric that has objective measures that limit heterogeneity between raters. Conversely, the MG-ADL is a subjective report by the patient, though the point categories of function are distinct which can limit variability in intra- and interpatient reports. It is also worth noting that MG-ADL has been the primary endpoint for other recent MG therapies including efgartigimod, ravulizumab, and eculizumab. The minimal clinically important difference (MCID) for MG-ADL is 2 points.[5]

Patients were stratified by their antibody type. Overall, 11% (n=21) of all participants were MuSK+. This is substantially higher than efgartigimod's phase III trial which only had 4% (n=6) of its population as MuSK+.[6] Similar to the rozanolixizumab phase II trial, the vast majority of patients (95%) were MGFA class II or III, about half were on steroids (65%) and/or immunosuppressants (52%), and most were on cholinesterase inhibitors (86%). The primary endpoint was met: both rozanolixizumab 7 mg/kg and 10 mg/kg had a significant improvement in the MG-ADL score at day 43 compared to placebo. There was

also a statistically significant improvement in all secondary efficacy outcomes for both rozanolixizumab doses. Full results are in Table 1. The efficacy seen across doses is relevant as FDA-approved dosing is a set dose based on weight ranges rather than a mg/kg dose. All FDA-approved doses fall in the 7-10mg/kg range, depending on the weight of the patient.

Open Label Extension (OLE)[7]

Patients who completed treatment in rozanolixizumab's phase III trial were eligible to continue in the OLE (NCT04124965). This OLE is completed, though results are not yet published. The protocol does refer to a 52-week "treatment period" and 8-week observational period. Dosing groups appear to have been maintained at 7mg/kg and 10mg/kg. However, it is unclear with the available information if breaks were taken between 6-week treatment cycles as is indicated in the current prescribing information for this medication. Of the original 71 enrolled, only 8 patients completed this entire study. The main reason for not completing was enrollment in another OLE (NCT04650854) which is still pending, but has clearly stated dosing of 6-week cycles. Thus, this still-pending OLE will likely be the more relevant OLE to long-term risks of the labeled dosing for rozanolixizumab.

Table 1: Efficacy results from phase III clinical trial[4]

Study	Results
MycarinG Phase III trial N = 200	All results described as least-squares mean change from baseline to day 43, except where indicated:

Primary:

	PBO	Rozanolixizumab 7 mg/kg	7mg/kg vs. PBO treatment difference	Rozanolixizumab 10 mg/kg	10mg/kg vs. PBO treatment difference
	n=67	n=66		n=67	
MG-ADL	-0.78	-3.37	-2.59* (-4.09, -1.25) p<0.0001	-3.4	-2.62* (-3.99, -1.16) p<0.0001

Secondary:

	PBO	Rozanolixizumab 7 mg/kg	7mg/kg vs. PBO treatment difference	Rozanolixizumab 10 mg/kg	10mg/kg vs. PBO treatment difference
	n=67	n=66		n=67	
MGC	-2.03	-5.93	-3.9* (-6.63, -1.25) p=0.0004	-7.55	-5.53* (-8.3, -2.97) p<0.0001
QMG	-1.92	-5.4	-3.48* (-5.61, -1.58) p<0.0001	-6.67	-4.76* (-6.82, -2.86) p<0.0001
MG Symptoms PRO: Muscle Weakness Fatigability	-10.59	-23.03	-12.44* (-21.8, -4.09) p=0.0003	-25.75	-15.16* (-23.6, -6.45) p<0.0001
MG Symptoms PRO: Physical Fatigue	-10.64	-19.29	-8.65* (-18.06, -0.13) p=0.012	-25.46	-14.82* (-23.76, -5.94) p=0.0002
MG Symptoms PRO: Bulbar Muscle Weakness	-3.52	-14.84	-11.32* (-18.96, -5) p=0.0001	-14.22	-10.71* (-17.79, -4) p=0.0001

	MG-ADL responders	31%	72%	----	69%	----

MCG=Myasthenia Gravis Composite
MG Symptoms PRO=Myasthenia Gravis Symptoms Patient Reported Outcome
*statistically significant

Safety Considerations[2,4,8]

Safety Results from Clinical Trials:

- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings / precautions**:
    - Infection risk: Rozanolixizumab may increase the risk of infection. It is recommended that this medication be avoided in active infection, which may mean delaying or holding treatment until infection resolves.
    - Vaccination considerations: Live or live-attenuated vaccines are not recommended during treatment with rozanolixizumab.
    - Aseptic Meningitis: this occurred in one patient in the gMG clinical trials and 2 patients in clinical trials for other neurologic indications (for which rozanolixizumab is not currently approved). All three cases led to hospitalization and discontinuation of rozanolixizumab.
    - Hypersensitivity: including angioedema and rash. It is recommended that patients be monitored for 15 minutes after administration for possible development of hypersensitivity reactions.
- **Adverse reactions**
    - **Common** – Adverse reactions occurring in 10% or more of patients on rozanolixizumab across clinical trials were: headache, infection, diarrhea, pyrexia, hypersensitivity reactions, and nausea.
    - **Serious Adverse events / Deaths:** no deaths occurred in rozanolixizumab gMG clinical trials. In the phase III trial, there were 3 patients on rozanolixizumab (1 on 7mg/kg and 2 on 10mg/kg) who experienced MG worsening that required hospital admission. There were no cases of MG crisis in the trial.

Other Considerations

- **Pregnancy and Lactation** – Safety data of rozanolixizumab during pregnancy and lactation is limited. Maternal IgG is known to be present in human milk (rozanolixizumab's mechanism of action reduces serum IgG levels).

Other Therapeutic Options

Alternative treatments for gMG are listed in tables 2 and 3 below:

Table 2 Treatment Alternatives – newer MG agents

Drug	Formulary status	Clinical Guidance	Other Considerations
Rozanolixizumab-noli (RYSTIGGO®) Neonatal Fc Receptor Antagonist	TBD	Effective in generalized MG patients who are AChR+ and MuSK+	Headache, infection, diarrhea, pyrexia, hypersensitivity reactions, and nausea. Subcutaneous infusion given weekly for 6 weeks. Repeated as needed no more than 63 days from start of previous cycle. Repeat cycles may be common as MG symptoms can return to baseline as soon as 8 weeks after stopping treatment. Efficacy and safety of long-term chronic therapy unknown at this time (OLE study pending).
Efgartigimod (Vyvgart®) Neonatal Fc Receptor Antagonist	NF, CFU	Effective in generalized MG patients who are AChR+ Studied in a very small number of other MG subtypes and improvement was minimal. As a subgroup, it was too small to be evaluated for statistical significance.	Allergic reactions, headache, infections, leukopenia, myalgia. IV infusion given weekly for 4 weeks. Repeated as needed no more than 50 days from start of previous cycle. Repeat cycles are common as MG symptoms can return to baseline as soon as 8 weeks after starting a 4-week cycle. Efficacy and safety of long-term chronic therapy not studied.
Ravulizumab-cwvz (Ultomiris®) Complement C5 Inhibitor	NF, CFU	Effective in generalized MG patients who are AChR+	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, diarrhea, headache IV infusion with weight-based dosing every 8 weeks, starting 2 weeks after the loading dose.
Eculizumab (Soliris®) Complement C5 Inhibitor	NF, CFU	Effective in refractory generalized MG patients who are AChR+	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, headaches, musculoskeletal pain IV infusion given weekly for 4 weeks then every 2 weeks.

Table 3 Treatment Alternatives – Other Chronic Immunotherapies

Drug	Formulary status	Time to onset of effect	Time to maximal effect
Azathioprine	F	12 months	1-2 years
Cyclosporine	F	6 months	7 months
Mycophenolate mofetil	F	6-12 months	1-2 years
Prednisone	F	2-3 weeks	5-6 months
Tacrolimus	F	6 months	12 months
IVIg	F	immediate	
Rituximab (stronger evidence in MuSK+ gMG)	F (biosimilar rituximab-pvvr)	6-12 months	7-16 months
Plasma exchange	Non-pharmacy product	immediate	

Projected Place in Therapy

- Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder. The disease is characterized by fatigable weakness cause by antibodies that interfere with skeletal muscle signaling at the neuromuscular junction. Symptoms can be limited to the eyes (ocular MG) or systemic (generalized MG, gMG). In its most severe case, gMG can result in respiratory depression or respiratory failure.
- It is estimated that there are fewer than 50,000 people with MG in the United States.[9] In FY22, there were 6,396 Veterans with MG who sought care at VA.
- Rozanolixizumab is the first MG therapy FDA approved for MuSK+ gMG as well as AChR+ gMG. In the MycarinG trial, rozanolixizumab had significant improvement in all primary and secondary outcomes including clinically significant improvement in MG-ADL and QMG scores.
- Rozanolixizumab joins efgartigimod in the neonatal Fc receptor antagonist class. Like efgartigimod, rozanolixizumab is dosed in cycles and provides fast-onset steroid-sparing control of gMG symptoms.
- Rozanolixizumab could be considered as short-term bridge therapy to initiation or switch of chronic immunosuppressant therapy in patients with gMG who are AChR+ or MuSK+.
- Alternatively, rozanolixizumab offers a steroid-sparing chronic treatment option to consider in AChR+ or MuSK+ gMG patients when other traditional oral immunosuppressants like azathioprine, mycophenolate, and/or steroids are ineffective.
- Rozanolixizumab should not be used with other IgG-affecting agents for chronic management including intravenous immunoglobulin (IVIg) or efgartigimod.
- There is no evidence to support the use of rozanolixizumab in other antibody types of MG including LRP4+ and seronegative disease.

References

1. Kiessling P, Lledo-Garcia R, Watanabe S, et al. The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase I study. Sci Transl Med. 2017 Nov 1; 9(414):eaan1208.
2. Bril V, Benatar M, Andersen H, et al. Efficacy and safety of rozanolixizumab in moderate to severe generalized myasthenia gravis. Neurology. 2021; 96:e853-65
3. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. Muscle Nerve 2014;49:661-665.
4. Bril V, Druzdz A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalized myasthenia gravis (Mycarin G): a radomised, double-blind, placebo-controlled, adaptive phase 3 study. Lancet Neurol 2023; 22(5): 383–94
5. Muppidi S. The myasthenia gravis–specific activities of daily living profile. Ann N Y Acad Sci 2012;1274:114-119.
6. Howard JF, Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021;20(7):526–536
7. A study to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab in adult patients with generalized myasthenia gravis. ClinicalTrials.gov Identifier: NCT04124965. Updated September 5, 2023. Accessed October 4, 2023 https://clinicaltrials.gov/study/NCT04124965?cond=Myasthenia%20Gravis&intr=Rozanolixizumab&term=NCT04124965
8. Rozanolixizumab (RYSTIGGO®) [Prescribing Information] UCB. Smyrna, GA; June 2023
9. National Institutes of Health (NIH) Genetic and Rare Diseases (GARD). Myasthenia Gravis. Updated February 2023. Accessed October 4, 2023 https://rarediseases.info.nih.gov/diseases/7122/myasthenia-gravis

Prepared November 2023. Contact person: Natasha Antonovich, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)