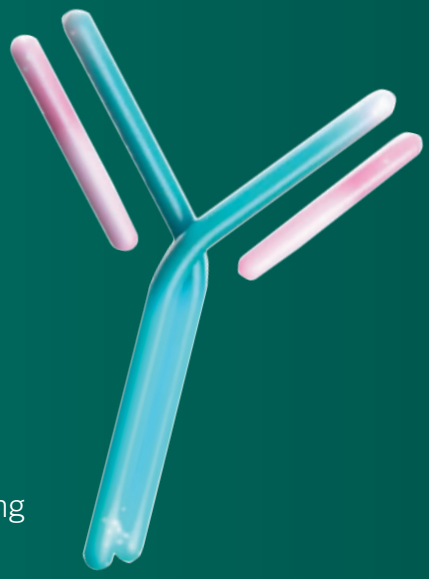
Pharmacokinetic and Pharmacodynamic Analysis of ULTOMIRIS® (ravulizumab-cwvz)

in Anti-AChR Antibody-Positive gMG

This brochure can only be provided after, or in conjunction with, the detailing of the CHAMPION-MG clinical trial



INDICATION

ULTOMIRIS is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

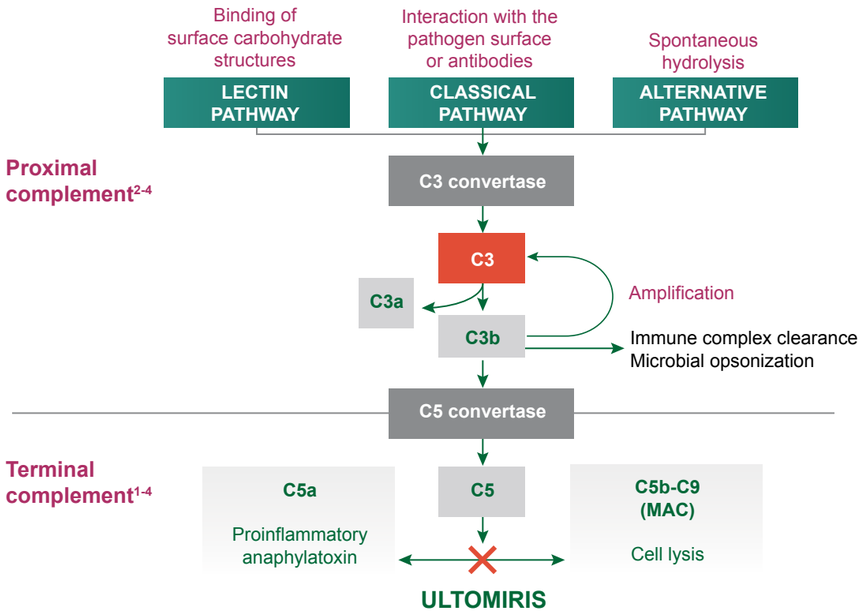
Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

Please see Important Safety Information throughout and the full Prescribing Information for ULTOMIRIS® (ravulizumab-cwvz), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, accompanying this material.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

US/ULT-g/0228 V2 04/2024

ULTOMIRIS® (ravulizumab-cwvz) Targets C5 to Inhibit Terminal Complement Activity[1]



- Binding of anti-AChR antibodies to AChR triggers activation of the complement system[5]
- Terminal complement activation results in cleavage of C5 into C5a and C5b[6]
- C5a leads to inflammation, while C5b binds to other complement proteins to form the MAC[5]
- MAC formation results in destruction to the NMJ[5,6]

- ULTOMIRIS is a monoclonal antibody that inhibits C5, preventing cleavage into C5a and C5b[1]
- This prevents formation of the MAC[1]

The precise mechanism by which ULTOMIRIS exerts its therapeutic effect in gMG patients is not known[1]

Abbreviations: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; MAC, membrane attack complex; NMJ, neuromuscular junction.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

CHAMPION-MG Evaluated the Change in MG-ADL Total Score From Baseline in Patients Treated With ULTOMIRIS® (ravulizumab-cwvz) vs Placebo

CHAMPION-MG was a phase 3, randomized, double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate efficacy and safety of ULTOMIRIS in 175 adults with anti-AChR antibody-positive gMG at 35 sites across 13 countries[7]

Primary endpoint[7]

Change from baseline to Week 26 in MG-ADL total score

Key secondary endpoint[7]

Change from baseline to Week 26 in QMG total score

Exploratory analysis[8]

PK/PD properties of ULTOMIRIS were studied as exploratory objectives

Key inclusion criteria[1,7]

- MGFA clinical classification class II-IV
- gMG (diagnosed for at least 6 months) with a positive serologic test for anti-AChR antibodies
- MG-ADL total score of ≥6
- Vaccination against meningococcal infections
- Stable doses of concomitant ISTs, if on a treatment regimen upon study entry

Key exclusion criteria[7]

- Any active or untreated thymoma or history of thymic carcinoma or thymic malignancy
- History of thymectomy, thymomectomy, or any thymic surgery ≤12 months before screening
- Clinical features consistent with MG crisis/exacerbation or clinical deterioration at the time of screening visit or any time before randomization
- IVIg or PE within the 4 weeks before randomization (Day 1)
- Rituximab within the 6 months before screening
- Any previous treatment with complement inhibitors

Abbreviations: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; ISTs, immunosuppressive therapies; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; PD, pharmacodynamics; PE, plasma exchange; PK, pharmacokinetics; QMG, Quantitative Myasthenia Gravis.

PK/PD Exploratory Analysis Study Design

Eligibility[8]

- All 86 patients who received ULTOMIRIS® (ravulizumab-cwvz) in the CHAMPION-MG study were included in the PK/PD analysis

Dosing[1,8]

Body weight range	Loading dose, mg	Maintenance dose, mg	Minimum infusion time[a]		Dosing interval
			Loading dose, min	Maintenance dose, min	
40 kg (88 lb) to <60 kg (132 lb)	2400	3000	48	54	Every 8 weeks, starting 2 weeks after initial loading dose
60 kg (132 lb) to <100 kg (220 lb)	2700	3300	36	42	
≥100 kg (220 lb)	3000	3600	24	30	

[a]If an adverse reaction occurs during the administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician.[1]

Follow-up[8]

- At baseline and weeks **2, 10, 18, and 26,** blood samples were obtained within 30 minutes **before infusion** to measure **baseline** and **trough levels** of antidrug antibodies, serum free C5, and serum ULTOMIRIS
- For **peak posttreatment** PK/PD analysis, blood samples were obtained within 30 minutes **after infusion** at baseline and **weeks 2, 10, 18, and 26**

Abbreviations: MG, myasthenia gravis; PD, pharmacodynamics; PK, pharmacokinetics.

US/ULT-g/0228 V2 04/2024

PK/PD Exploratory Analysis Methods

Serum Free C5 Concentration

- **Pharmacodynamics (PD) is the study of the effect of a drug on body processes[9]**
- Measured via validated microfluidics assay with fluorescence detection using ULTOMIRIS to capture free C5, with an LLOQ of 0.0183 µg/mL[8]
- Serum free C5 concentration <0.5 µg/mL represents complete terminal complement inhibition[8]

Serum ULTOMIRIS® (ravulizumab-cwvz) Concentration

- **Pharmacokinetics (PK) is the study of the effect of body processes on a drug[9]**
- Quantified via validated liquid chromatography with tandem mass spectrometry, with an LLOQ of 1.00 µg/mL[8]
- The target serum concentration of ULTOMIRIS was >175 µg/mL[8]

Abbreviations: LLOQ, lower limit of quantification; PD, pharmacodynamics; PK, pharmacokinetics.

US/ULT-g/0228 V2 04/2024

Baseline Patient Characteristics in the CHAMPION-MG Trial[8]

Patient Characteristics

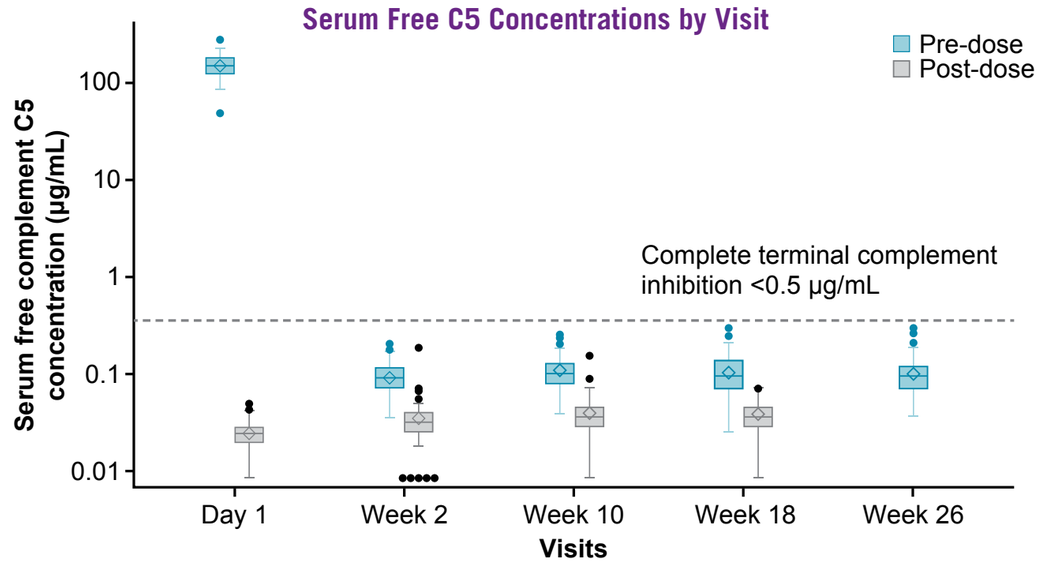
Characteristics[7,8]	Data value
Age at MG diagnosis, mean (SD)	48.6 (18.5)
Age at first study dose, mean (SD), years	58.0 (13.8)
Weight, mean (SD), kg	91.6 (23.4)
Baseline MG-ADL score, mean (SD)	9.1 (2.6)
Baseline QMG score, mean (SD)	14.8 (5.2)
Race, n (%)	
White	67 (78)
Asian	15 (17)
African American	2 (2)
Unreported	2 (2)

- At CHAMPION-MG study entry, the majority of patients were receiving ISTs[7,8]

Abbreviations: ISTs, immunosuppressive therapies; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; SD, standard deviation; QMG, Quantitative Myasthenia Gravis.

Serum Free C5 Concentrations During CHAMPION-MG[8]

Complete terminal complement inhibition was observed as of study Day 1 and was shown throughout 26 weeks for 100% of patients



Adapted from Vu T, et al. *J Neurol.* Published online March 9, 2023. doi:10.1007/s00415-023-11617-1

Note: No inferences of efficacy or safety can be made from this data.

- Administration of ULTOMIRIS achieved immediate and complete terminal complement inhibition (serum free C5 <0.5 µg/mL)
- Free C5 concentrations below LLOQ were analyzed as 0.00915 µg/mL
- Mean baseline serum free C5 concentration (pre-dose) was 153.6 (SD 37.0) µg/mL
- ADA titers were low and transient, with no apparent effect on PK or PD

Abbreviations: ADA, antidrug antibody; LLOQ, lower limit of quantification; MG, myasthenia gravis; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

Learn more about ULTOMIRIS at
ULTOMIRISHCP.com

SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common adverse reactions in adult patients with gMG (incidence ≥10%) were diarrhea and upper respiratory tract infection. Serious adverse reactions were reported in 20 (23%) of patients treated with ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent serious adverse reactions were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers

Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Important Safety Information throughout and the full Prescribing Information for ULTOMIRIS® (ravulizumab-cwvz), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, accompanying this material.

Scan QR code or visit the link
https://bit.ly/3KEpmzp

References: 1. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Rother RP, Rollins SA, Mojcik CF, et al. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat Biotechnol.* 2007;25(11):1256-1264. doi:10.1038/nbt1344 **3.** Murphy K, Weaver C. *Janeway's Immunobiology.* 9th ed. Garland Science/Taylor & Francis Group LLC; 2016. **4.** Sheridan D, Yu ZX, Zhang Y, et al. Design and preclinical characterization of ALXN1210: a novel anti-C5 antibody with extended duration of action. *PLoS One.* 2018;13(4):e0195909. doi:10.1371/journal.pone.0195909 **5.** Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. *J Clin Invest.* 2006;116(11):2843-2854. doi:10.1172/JCI29894 **6.** Howard JF Jr. Myasthenia gravis: the role of complement at the neuromuscular junction. *Ann N Y Acad Sci.* 2018;1412(1):113-128. doi:10.1111/nyas.13522 **7.** Vu T, Meisel A, Mantegazza R, et al. Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. *NEJM Evid.* 2022;1(5). doi:10.1056/EVIDoa2100066 **8.** Vu T, Ortiz S, Katsuno M, et al. Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis. *J Neurol.* Published online March 9, 2023. doi:10.1007/s00415-023-11617-1 **9.** Marino M, Jamal Z, Zito PM. Pharmacodynamics. 2022. In: *StatPearls Internet.* StatPearls Publishing; 2023. Accessed March 20, 2023. https://www.ncbi.nlm.nih.gov/books/NBK50779

ALEXION®
AstraZeneca Rare Disease