▼ This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ULTOMIRIS® (RAVULIZUMAB RCH)

100 MG/ML SOLUTION FOR INTRAVENOUS INFUSION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
ULTOMIRIS increases the risk of meningococcal infections.

- **Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognised and treated early (see *section 4.4 Special Warnings and Precautions for Use*).**
- **Immunise patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection (see *section 4.4 Special Warnings and Precautions for Use* for additional guidance on the management of the risk of meningococcal infection).**
- **Refer to the most current edition of the Australian Immunisation Handbook for meningococcal vaccination guidelines.**
- **Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected. Patients should be advised about the signs and symptoms of meningococcal infection and to seek medical care immediately if they occur.**

1 NAME OF THE MEDICINE

Ravulizumab *rch*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ULTOMIRIS is a formulation of ravulizumab *rch* which is a long acting humanised monoclonal Immunoglobulin (Ig) G2/4K antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

ULTOMIRIS is supplied as a single use vial containing 100 mg/mL (300 mg in 3 mL or 1100 mg in 11 mL) of ravulizumab *rch*.

For the full list of excipients, see *section 6.1 List of Excipients*.

3 PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion.

ULTOMIRIS 100 mg/mL is a translucent, clear to yellowish colour, pH 7.4 solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ULTOMIRIS is indicated:

- for the treatment of patients with Paroxysmal Nocturnal Haemoglobinuria (PNH)
- for the treatment of patients with Atypical Haemolytic Uraemic Syndrome (aHUS)
- as an add-on to standard therapy for the treatment of adult patients with generalised myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.
- for the treatment of adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive.
  ULTOMIRIS is not intended for the acute treatment of a NMOSD relapse.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

ULTOMIRIS should be administered by a healthcare professional and under appropriate medical supervision.

Adult patients with PNH, aHUS, gMG or NMOSD with body weight ≥40 kg

The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. Maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

For patients switching from SOLIRIS® (eculizumab *rmc*) to ULTOMIRIS, the loading dose of ULTOMIRIS should be administered 2 weeks after the last eculizumab *rmc* maintenance infusion (or 1 week after the last eculizumab *rmc* induction infusion), and then maintenance doses are administered once every 8 weeks, starting 2 weeks after loading dose administration, as shown in Table 1.

Table 1 ULTOMIRIS Weight-Based Dosing Regimen

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose* (mg)	Dosing interval
≥ 40 to < 60	2400	3000	Every 8 weeks
≥ 60 to < 100	2700	3300	Every 8 weeks
≥ 100	3000	3600	Every 8 weeks

* First maintenance dose is administered 2 weeks after loading dose

Paediatric patients with PNH and aHUS with body weight ≥5kg

Paediatric patients who weigh ≥ 40 kg are treated with the adult dosing recommendations above. The weight-based dosing recommendation and dosing interval for paediatric patients < 40 kg are shown in Table 2, with maintenance doses starting 2 weeks after loading dose administration.

For patients switching from eculizumab to ULTOMIRIS, the loading dose of ULTOMIRIS should be administered 2 weeks after the last eculizumab maintenance infusion (or 1 week after the last eculizumab induction infusion), and then maintenance doses should be administered per weight-based dosing regimen shown in Table 2, starting 2 weeks after loading dose administration.

Table 2 ULTOMIRIS Weight-Based Dosing Regimen for Paediatric Patients < 40 kg

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose* (mg)	Dosing Interval
≥ 5 to < 10	600	300	Every 4 weeks
≥ 10 to < 20	600	600	Every 4 weeks
≥ 20 to < 30	900	2100	Every 8 weeks
≥ 30 to < 40	1200	2700	Every 8 weeks

* First maintenance dose is administered 2 weeks after loading dose

ULTOMIRIS should be administered at the recommended dosage regimen time points. The dosing schedule is allowed to vary occasionally by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS) but the subsequent dose should be administered according to the original schedule.

PNH is a chronic disease and treatment with ULTOMIRIS is recommended to continue for the patient's lifetime, see *section 4.4 Special Warnings and Precautions for Use; Monitoring after ULTOMIRIS Discontinuation*.

In aHUS, ULTOMIRIS treatment should be a minimum duration of 6 months. Due to the heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualised. Patients who are at higher risk for thrombotic microangiopathy (TMA) recurrence, as determined by the treating physician (or clinically indicated) may require chronic therapy, see *section 4.4 Special Warnings and Precautions for Use; Monitoring after ULTOMIRIS Discontinuation*.

Supplemental dosing following treatment with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg).

Plasma exchange (PE), plasmapheresis (PP) and intravenous immunoglobulin (IVIg) have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP or IVIg (Table 3).

Table 3 Supplemental Dose of ULTOMIRIS Dose after PE, PP, or IVIg

Body Weight Group (kg)	Most Recent ULTOMIRIS Dose (mg)	Supplemental Dose (mg) Following Each PP or PE Session	Supplemental Dose (mg) Following complete IVIg Cycle
≥ 40 to < 60	2400	1200	600
	3000	1500	
≥ 60 to < 100	2700	1500	600

Body Weight Group (kg)	Most Recent ULTOMIRIS Dose (mg)	Supplemental Dose (mg) Following Each PP or PE Session	Supplemental Dose (mg) Following complete IVIg Cycle
≥ 100	3300	1800	600
	3000	1500	
	3600	1800	
Timing of ULTOMIRIS Supplemental Dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

Abbreviations: IVIg = intravenous immunoglobulin; PE = plasma exchange; PP = plasmapheresis

Please refer to Table 6 for additional information concerning supplemental dose administration after PE, PP, or IVIg.

Preparation for Administration

ULTOMIRIS must be diluted to a final concentration of 50 mg/mL.

Aseptic technique must be used.

Prepare ULTOMIRIS as follows:

- The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose.
- Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
- The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using 0.9% sodium chloride injection USP as diluent. Refer to the administration reference tables below.
- The product should be mixed gently. It should not be shaken.
- After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Each vial of ULTOMIRIS is intended for single use only.

Table 4 Loading Dose Administration Reference Table

Indication	Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)[b]	Volume of NaCl Diluent (mL)	Total Volume (mL)	Minimum Infusion Duration Minutes (hours)
PNH/aHUS	≥ 5 to < 10	600	6	6	12	85 (1.4)
	≥ 10 to < 20	600	6	6	12	45 (0.8)
	≥ 20 to < 30	900	9	9	18	35 (0.6)
	≥ 30 to < 40	1200	12	12	24	31 (0.5)
PNH/aHUS/ gMG/ NMOSD	≥ 40 to < 60	2400	24	24	48	45 (0.8)
	≥ 60 to < 100	2700	27	27	54	35 (0.6)
	≥ 100	3000	30	30	60	25 (0.4)

[a] Body weight at time of treatment; [b] The volume in each ULTOMIRIS vial is either 3 mL or 11 mL;
[c] ULTOMIRIS should only be diluted using 0.9% sodium chloride injection USP

Table 5 Maintenance Dose Administration Reference Table

Indication	Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)[b]	Volume of NaCl Diluent[c] (mL)	Total Volume (mL)	Minimum Infusion Duration Minutes (hours)
PNH/aHUS	≥ 5 to < 10	300	3	3	6	45 (0.8)
	≥ 10 to < 20	600	6	6	12	45 (0.8)
	≥ 20 to < 30	2100	21	21	42	75 (1.3)
	≥ 30 to < 40	2700	27	27	54	65 (1.1)
PNH/aHUS/ gMG/ NMOSD	≥ 40 to < 60	3000	30	30	60	55 (0.9)
	≥ 60 to < 100	3300	33	33	66	40 (0.7)
	≥ 100	3600	36	36	72	30 (0.5)

[a]Body weight at time of treatment; [b]The volume in each ULTOMIRIS vial is either 3 mL or 11 mL;
[c]ULTOMIRIS should only be diluted using 0.9% sodium chloride injection USP

Table 6 Supplemental Dose Administration Reference Table (after PE, PP, or IVIg)

Body Weight Range (kg)[a]	Supplemental Dose (mg)	ULTOMIRIS Volume (mL)[b]	Volume of NaCl Diluent[c] (mL)	Total Volume (mL)	Minimum Infusion Duration Minutes (hours)
≥ 40 to < 60	600*	6	6	12	15 (0.25)
	1200	12	12	24	25 (0.42)
	1500	15	15	30	30 (0.5)
≥ 60 to < 100	600*	6	6	12	12 (0.20)
	1500	15	15	30	22 (0.36)
	1800	18	18	36	25 (0.42)
≥ 100	600*	6	6	12	10 (0.17)
	1500	15	15	30	15 (0.25)
	1800	18	18	36	17 (0.28)

* For gMG and NMOSD indication only. [a]Body weight at time of treatment; [b]The volume in each ULTOMIRIS vial is either 3 mL or 11 mL; [c]ULTOMIRIS should only be diluted using 0.9% sodium chloride injection USP

Please refer to Table 3 for selection of ULTOMIRIS supplemental dose.

Method of Administration

Do not administer as an intravenous push or bolus injection.

The prepared solution should be administered immediately following preparation. Refer to the administration reference tables above for minimum infusion duration. If the medicinal product is not used immediately after reconstitution, storage times must not exceed 24 hours at 2°C – 8°C. The prepared solution can be stored for 4 hours at room temperature taking into account the expected infusion time. Infusion must be administered through a 0.2 µm filter.

If an adverse reaction occurs during the administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician. Patients should be monitored post infusion for signs or symptoms of an infusion-related reaction.

Dosage Adjustment

Paediatric population

ULTOMIRIS has not been studied in PNH patients who weigh less than 30 kg. The posology to be used in paediatric patients with PNH who weigh less than 30 kg is identical to the weight-based

dosing recommendations provided for paediatric patients with aHUS based on pharmacokinetic/pharmacodynamic (PK/PD) data available in aHUS and PNH patients treated with ULTOMIRIS.

ULTOMIRIS has not been studied in paediatric patients with gMG or NMOSD.

Elderly (> 65 years old)

No dose adjustment is required for patients with PNH, aHUS, gMG or NMOSD aged 65 years and over. There is no evidence indicating any special precautions are required for treating an elderly population although experience with ULTOMIRIS in elderly patients with PNH, aHUS, gMG or NMOSD in clinical studies is limited.

Patients with Aplastic Anaemia

ULTOMIRIS may be administered to patients with PNH treated with concomitant medications for aplastic anaemia (including immunosuppressive therapies). There is no evidence indicating any special precautions are required for treating patients with aplastic anaemia.

Renal Impairment

The clinical trials of ULTOMIRIS in patients with aHUS included patients with renal impairment, some of whom were receiving dialysis. No dose adjustment is required for patients with renal impairment (see *section 5.1 Pharmacodynamic Properties* and *section 5.2 Pharmacokinetic Properties, Special Populations*).

Hepatic Impairment

The safety and efficacy of ULTOMIRIS have not been studied in patients with hepatic impairment, however pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

Known hypersensitivity to ULTOMIRIS or to any of the excipients listed in *section 6.1 List of Excipients*.

Do not initiate ULTOMIRIS therapy in patients:

- with unresolved *Neisseria meningitidis* infection, see *section 4.4. Special Warnings and Precautions for Use; Serious Meningococcal Infectio*n.
- who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Meningococcal Infection

Due to its mechanism of action, the use of ULTOMIRIS increases the patient's susceptibility to meningococcal infection/sepsis *(Neisseria meningitidis)*. Meningococcal infection due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to initiating ULTOMIRIS unless the risk of delaying ULTOMIRIS outweighs the risks of developing meningococcal infection. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135 and B where available, are recommended to reduce the risk of infection with the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current medical guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. The prescriber and patient should discuss the potential role of ongoing preventative antibacterials. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with ULTOMIRIS and other terminal complement inhibitors. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. Physicians should provide patients with a Patient Information Brochure and a Patient Safety Card.

Immunisation

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Patients below the age of 18 years old must be vaccinated against *Haemophilus influenzae* and pneumococcal infections and need to adhere strictly to the national vaccination recommendations for their age group.

Other Systemic Infections

ULTOMIRIS therapy should be administered with caution to patients with active systemic infections. ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially infections caused by *Neisseria* species and encapsulated bacteria. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported in patients treated with ULTOMIRIS.

Patients should be provided with a Patient Information Brochure to increase their awareness of potential serious infections and their signs and symptoms.

Physicians should advise patients about gonorrhoea prevention.

Infusion Reactions

Administration of ULTOMIRIS may result in systemic infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials infusion reactions were common (1.9%). They were mild to moderate in severity and transient. These events included back pain, abdominal pain, muscle spasms, drop in blood pressure, elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. In case of systemic infusion reaction, infusion of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur (see *section 4.8 Adverse Effects (Undesirable Effects), Post-marketing Experience*).

Immunogenicity

Treatment with any therapeutic protein may induce an immune response. In ULTOMIRIS studies (PNH studies [n = 488], aHUS studies [n = 92], a gMG study [n = 167] and a NMOSD study [n=58]), treatment-emergent anti-drug antibodies were reported in 10 patients (1.2%), 6 with PNH, 2 with aHUS and 2 with gMG. Of these, only 2 (PNH) were persistent, at low titres, and neither correlated with clinical response or adverse events.

Monitoring After ULTOMIRIS Discontinuation

Treatment discontinuation for PNH

PNH is a chronic disease and treatment with ULTOMIRIS is recommended to continue for the patient's lifetime.

If patients with PNH discontinue treatment with ULTOMIRIS, they should be closely monitored for signs and symptoms of haemolysis, identified by elevated lactate dehydrogenase (LDH) along with sudden decrease in PNH clone size or haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Any patient who discontinues ULTOMIRIS should be monitored for at least 16 weeks to detect haemolysis and other reactions. If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Treatment discontinuation for aHUS

There are no specific data on ULTOMIRIS discontinuation. Severe TMA complications were observed following SOLIRIS discontinuation in aHUS clinical studies (in some patients up to 127 weeks after discontinuation) and can occur at any time.

If patients must discontinue treatment with ULTOMIRIS, they should be closely monitored for signs and symptoms of TMA on an on-going basis. Monitoring may be insufficient to predict or prevent TMA complications.

TMA complications post-discontinuation can be identified if any of the following is observed;

(i) At least two of the following laboratory results observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment (results should be confirmed by a second measurement)

(ii) Any one of the following symptoms of TMA: a change in mental status or seizures or other extra-renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea; or thrombosis.

If TMA complications occur after ULTOMIRIS discontinuation, re-initiation of ULTOMIRIS treatment should be considered, beginning with the loading dose and maintenance dose *(*see *Section 4.2 Dose and Method of Administration)*.

Treatment discontinuation for gMG

As gMG is a chronic disease, patients benefiting from ULTOMIRIS who discontinue treatment should be monitored for symptoms of the underlying disease. If symptoms of gMG occur after discontinuation, consider restarting treatment with ULTOMIRIS.

Treatment discontinuation for NMOSD

As NMOSD is a chronic disease, patients benefiting from ULTOMIRIS treatment who discontinue treatment should be monitored for symptoms of NMOSD relapse. If symptoms of NMOSD relapse occur after discontinuation, consider restarting treatment with ULTOMIRIS.

Use in the Elderly

ULTOMIRIS may be administered to patients with PNH, aHUS, gMG or NMOSD aged 65 years and over. There is no evidence indicating any special precautions are required for treating an elderly population.

Paediatric Use

Based on data available in aHUS and PNH patients treated with ULTOMIRIS, the efficacy and safety profile in paediatric patients with body weight ≥ 5 kg is expected to be similar to that of adults.

Use of ULTOMIRIS in paediatric PNH patients with body weight < 30 kg is based on extrapolation of PK/PD, efficacy and safety data from aHUS and PNH clinical studies.

ULTOMIRIS has not been studied in paediatric patients with gMG or NMOSD.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS. See Section 4.2 for guidance in case of concomitant PE, PP, or IVIg treatment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on fertility have been conducted specifically with ULTOMIRIS.

A study in mice with a surrogate terminal complement inhibitor (murine anti-C5) antibody identified no adverse effect on fertility of the treated females or males. Use of a surrogate molecule was required as ULTOMIRIS does not recognise the form of the pharmacological target present in laboratory animal species.

Use in Pregnancy – Category B2

No clinical data on exposed pregnancies are available.

No studies on embryofetal development have been conducted specifically with ULTOMIRIS. A study in mice with a murine surrogate terminal complement inhibitory (anti-C5) antibody given during the period of organogenesis identified no clear treatment-related findings in fetuses of mice exposed to 60 mg/kg/week but is of limited predictive value. When exposure to the murine antibody occurred from the time of implantation to the end of lactation, a slightly higher number of male offspring became moribund or died in the group given 60 mg/kg/week. The relevance to use of ULTOMIRIS is unclear. Human IgG are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in the fetal circulation.

Women of childbearing potential should use effective contraception methods during treatment and for 8 months after treatment.

Use in Lactation

It is unknown whether ULTOMIRIS is excreted into human milk. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment and for 8 months after treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

The most common adverse drug reactions across all clinical trials are headache, upper respiratory tract infection, nasopharyngitis, diarrhoea, pyrexia, nausea, arthralgia, backpain, fatigue, abdominal pain, urinary tract infection and dizziness. The most serious adverse reactions in patients in clinical trials were meningococcal infection and meningococcal sepsis.

The clinical safety data described below were obtained with a lower concentration (10 mg/mL) formulation of ULTOMIRIS.

Table 7 gives the adverse reactions observed from clinical trials.

Adverse reactions are listed by MedDRA System Organ Class (SOC) and frequency, using the following convention: very common (≥ 1/ 10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7 Adverse Drug Reactions from Clinical Trials

MedDRA System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Infections and infestations	Urinary tract infection[a] Upper respiratory tract infection, Nasopharyngitis		Meningococcal infection[b], Disseminated Gonococcal infection[c]
Nervous system disorders	Dizziness, Headache		
Gastrointestinal disorders	Diarrhoea, Nausea, Abdominal pain	Vomiting, Dyspepsia	
Skin and subcutaneous tissue disorders		Urticaria, Pruritus, Rash	
Musculoskeletal and connective tissue disorders	Arthralgia, Back pain	Myalgia, Muscle spasms	
General disorders and administration site conditions	Pyrexia, Fatigue	Influenza like illness, Chills, Asthenia	
Injury, poisoning and procedural complications		Infusion-related reaction	

[a] Urinary tract infection is a group term that includes Preferred Terms: Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, and Escherichia urinary tract infection.
[b] Meningococcal infection includes preferred terms of Meningococcal infection, Meningococcal sepsis, Meningococcal meningitis and Encephalitis meningococcal.
[c] Disseminated gonococcal infection includes preferred terms of disseminated gonococcal infection and gonococcal infection

Paroxysmal Nocturnal Haemoglobinuria (PNH)

Adult population with PNH

The data described below reflect exposure of 441 adult patients with PNH from the registration Phase 3 studies with a median treatment duration of 6 months for ULTOMIRIS and 6 months for SOLIRIS (eculizumab *rmc*).

Table 8 describes adverse events that occurred at a rate of 5% or more among patients treated with ULTOMIRIS in PNH studies.

Serious adverse events were reported in 15 (6.8%) patients with PNH receiving ULTOMIRIS. The serious adverse events in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse events were reported in more than 1 patient treated with ULTOMIRIS.

Table 8 Adverse Events Reported In 5% or More of ULTOMIRIS-Treated Patients in Complement Inhibitor Naïve and SOLIRIS-Experienced Adult Patients with PNH

Body System Adverse Event	**Number of Patients**	
	ULTOMIRIS (n = 222) n (%)	**SOLIRIS (n = 219) n (%)**
Gastrointestinal disorders		
Diarrhoea	19 (9)	12 (5)
Nausea	19 (9)	19 (9)
Abdominal pain	13 (6)	16 (7)
General disorders and administration site conditions		
Pyrexia	15 (7)	18 (8)
Infections and infestations		
Upper respiratory tract infection[a]	86 (39)	86 (39)
Musculoskeletal and connective tissue disorders		
Pain in extremity	14 (6)	11 (5)
Arthralgia	11 (5)	12 (5)
Nervous system disorders		
Headache	71 (32)	57 (26)
Dizziness	12 (5)	14 (6)

[a] Grouped term includes: Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhoea, Pharyngitis, and Upper respiratory tract inflammation

Paediatric population with PNH

In paediatric PNH patients (aged 9 to 17 years) included in the paediatric PNH Phase 3 study, the safety profile appeared similar to that observed in adult PNH patients and in paediatric and adult aHUS patients. The most common adverse events were abdominal pain and upper respiratory tract infections (refer to Table 9 below).

Table 9 Adverse Events Reported in 10% or More of ULTOMIRIS-Treated Paediatric PNH Patients in Study ALXN1210-PNH-304

Body System Adverse Event	**Treatment Naïve**	**SOLIRIS Experienced**	**Total**
	n=5 n (%)	**n=8 n (%)**	**n=13 n (%)**
Blood and lymphatic system disorders			
Anaemia	0 (0)	2 (25)	2 (15)
Gastrointestinal disorders			
Abdominal pain	0 (0)	3 (38)	3 (23)
Abdominal pain upper	0 (0)	3 (38)	3 (23)
Nausea	0 (0)	3 (38)	3 (23)
Constipation	0 (0)	2 (25)	2 (15)
Diarrhoea	0 (0)	2 (25)	2 (15)
General disorders and administration site conditions			
Fatigue	0 (0)	2 (25)	2 (15)
Pyrexia	1 (20)	1 (13)	2 (15)
Infections and infestations			
Upper Respiratory tract infection[a]	1 (20)	6 (75)	7 (54)
COVID-19	2 (40)	1 (13)	3 (23)
Urinary tract infection	0 (0)	2 (25)	2 (15)
Musculoskeletal and connective tissue disorders			
Pain in extremity	0 (0)	2 (25)	2 (15)
Nervous system disorders			
Headache	1 (20)	2 (25)	3 (23)

[a] Grouped term includes Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Rhinovirus infection, Viral pharyngitis, Rhinorrhea and Pharyngitis

atypical Haemolytic Uraemic Syndrome (aHUS)

The data described below reflect exposure of 58 adult and 31 paediatric patients with aHUS in single-arm trials who received ULTOMIRIS at the recommended dose and schedule.

Table 10, Table 11 and Table 12 describe the adverse events that occurred at a rate of 10% or more among patients treated with ULTOMIRIS in the aHUS studies.

Serious adverse events were reported in 54 (65.85%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse events reported in more than 3 patients (3.3%) treated with ULTOMIRIS were hypertension, pneumonia, diarrhoea and pyrexia. Five patients died during the ALXN1210-aHUS-311 study. The cause of death was sepsis in 2 patients, intracranial haemorrhage in 1 patient, pre-treatment cerebral arterial thrombosis in 1 patient that was excluded from the trial after a diagnosis of Shiga toxin *Escherichia coli* related haemolytic uraemic syndrome (STEC-HUS) and acute cardiac failure in 1 patient during the extension period.

Table 10 Adverse Events Reported in 10% or More of ULTOMIRIS-Treated Adult Patients with aHUS in Study ALXN1210-aHUS-311

Body System Adverse Event	N=58	
	All Grades*** (n=54) n (%)	≥ Grade 3 (n=19) n (%)
Blood and lymphatic system disorders		
Anaemia	10 (17)	0 (0)
Gastrointestinal disorders		
Diarrhoea	21 (36)	2 (3)
Vomiting	17 (29)	1 (2)
Nausea	17 (29)	1 (2)
Constipation	10 (17)	1 (2)
Abdominal pain	7 (12)	1 (2)
Abdominal pain upper	7 (12)	1 (2)
Dyspepsia	6 (10)	1 (2)
General disorders and administration site conditions		
Pyrexia	13 (22)	1 (2)
Oedema peripheral	11 (19)	0 (0)
Fatigue	9 (16)	0 (0)
Asthenia	7 (12)	2 (3)
Infections and infestations		
Upper respiratory tract infection*	21 (36)	1 (2)
Urinary tract infection	12 (21)	5 (9)
Gastrointestinal infection**	9 (16)	2 (3)
Pneumonia	7 (12)	3 (5)
Metabolism and nutrition disorders		
Hypokalaemia	7 (12)	2 (3)
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (28)	0 (0)
Back pain	7 (12)	1 (2)
Pain in extremity	7 (12)	0 (0)
Muscle spasms	6 (10)	0 (0)
Nervous system disorders		
Headache	25 (43)	1 (2)
Dizziness	7 (12)	0 (0)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic and mediastinal disorders		
Cough	12 (21)	0 (0)
Dyspnoea	12 (21)	1 (2)
Skin and subcutaneous tissue disorders		
Pruritis	7 (12)	0 (0)
Rash	7 (12)	0 (0)
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)
Hypotension	6 (10)	3 (5)

*Grouped term includes Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Rhinitis, Viral upper respiratory tract infection, Rhinovirus infection, Viral pharyngitis, Rhinorrhoea, and Oropharyngeal pain.

**Grouped term includes Gastroenteritis, Gastrointestinal infection, Enterocolitis infectious, Infectious colitis, and Enterocolitis.

***Graded per CTCAE v5.0.

Clinically relevant adverse reactions in <10% of patients include viral tonsillitis.

Table 11 Adverse Events Reported in 10% or More of ULTOMIRIS-Treated Paediatric Patients with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Event	N=34	
	All Grades** (n=33) n (%)	≥ Grade 3 (n=13) n (%)
Gastrointestinal disorders		
Vomiting	10 (29)	1 (3)
Diarrhoea	10 (29)	1 (3)
Abdominal pain	7 (21)	0 (0)
Constipation	5 (15)	0 (0)
Nausea	4 (12)	0 (0)
General disorders and administration site conditions		
Pyrexia	14 (41)	3 (9)
Infections and infestations		
Upper respiratory tract infection*	18 (53)	2 (6)
Gastrointestinal infection**	5 (15)	0 (0)
Pneumonia	4 (12)	2 (6)
Injury, poisoning and procedural complications		
Contusion	6 (18)	0 (0)
Musculoskeletal and connective tissue disorders		
Myalgia	4 (12)	0 (0)
Back pain	4 (12)	0 (0)
Nervous system disorders		
Headache	9 (26)	1 (3)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (21)	0 (0)
Epistaxis	4 (12)	0 (0)
Nasal congestion	4 (12)	0 (0)
Skin and subcutaneous tissue disorders		
Rash	4 (12)	0 (0)
Vascular disorders		
Hypertension	7 (21)	2 (6)

*Grouped term includes Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Rhinitis, Viral upper respiratory tract infection, Rhinovirus infection, Viral pharyngitis, Rhinorrhoea, and Oropharyngeal pain.
**Grouped term includes Gastroenteritis, Gastrointestinal infection, Enterocolitis infectious, Infectious colitis and Enterocolitis.
***Graded per CTCAE v5.0.

Clinically relevant adverse reactions in <10% of patients include viral infection.

Table 12 Adverse Events Reported in 10% or More of ULTOMIRIS-Treated Patients from Birth to 18 Years of Age with aHUS in Study ALXN1210-aHUS-312

	Age 0 to <2 (n=7)	Age 2 to <6 (n=10)	Age 6 to < 12 (n=7)	Age 12 to < 18 (n=10)	Total (n=34)
System Organ Class Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders					
Diarrhoea	2 (29)	2 (20)	2 (29)	4 (40)	10 (29)
Vomiting	2 (29)	4 (40)	2 (29)	2 (20)	10 (29)
Abdominal pain	0 (0)	2 (20)	3 (43)	2 (20)	7 (21)
Constipation	1 (14)	3 (30)	1 (14)	0 (0)	5 (15)
Nausea	0 (0)	1 (10)	2 (29)	1 (10)	4 (12)
General disorders and administration site conditions					
Pyrexia	1 (14)	5 (50)	4 (57)	4 (40)	14 (41)
Infections and infestations					
Upper respiratory tract infection*	2 (29)	7 (70)	5 (71)	4 (40)	18 (53)
Gastrointestinal infection**	0 (0)	4 (40)	0 (0)	1 (10)	5 (15)
Pneumonia	1 (14)	0 (0)	2 (29)	1 (10)	4 (12)
Injury, poisoning and procedural complications					
Contusion	0 (0)	2 (20)	3 (43)	1 (10)	6 (18)
Musculoskeletal and connective tissue disorders					
Back pain	0 (0)	0 (0)	2 (29)	2 (20)	4 (12)
Myalgia	1 (14)	0 (0)	2 (29)	1 (10)	4 (12)
Nervous system disorders					
Headache	0 (0)	1 (10)	5 (71)	3 (30)	9 (26)
Respiratory, thoracic and mediastinal disorders					
Cough	0 (0)	3 (30)	2 (29)	2 (20)	7 (21)
Epistaxis	0 (0)	0 (0)	2 (29)	2 (20)	4 (12)
Nasal congestion	1 (14)	0 (0)	3 (43)	0 (0)	4 (12)
Skin and subcutaneous tissue disorders					
Rash	1 (14)	0 (0)	3 (43)	0 (0)	4 (12)
Vascular disorders					
Hypertension	2 (29)	1 (10)	2 (29)	2 (20)	7 (21)

*Grouped term includes Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Rhinitis, Viral upper respiratory tract infection, Rhinovirus infection, Viral pharyngitis, Rhinorrhoea, and Oropharyngeal pain.

**Grouped term includes Gastroenteritis, Gastrointestinal infection, Entercolitis, Infectious colitis and Enterocolitis.

Clinically relevant adverse reactions in <10% of patients include viral infection.

Generalised Myasthenia Gravis (gMG)

The safety of ULTOMIRIS has been evaluated in 175 adult patients with gMG, including 169 patients who received at least one dose of ULTOMIRIS, 160 patients who were exposed for at least 6 months, and 150 who were exposed for at least 12 months (see *section 5.1, Pharmacodynamic Properties, Clinical Trials, Generalised Myasthenia Gravis*). In a randomised, double-blind, placebo-controlled trial (ALXN1210-MG-306), the most frequent adverse events (>10%) with ULTOMIRIS were diarrhoea and upper respiratory tract infection. Table 13 describes adverse events that occurred at a rate of 5% or more and at greater frequency than placebo.

Serious adverse events were reported in 20 (23%) patients with gMG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent serious adverse events 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 the discontinuation of ULTOMIRIS.

Table 13 Adverse Events Reported in ≥ 5% and at Greater Frequency than Placebo in ULTOMIRIS-treated Adult Patients with gMG in Study ALXN1210-MG-306

Body System Adverse Event	N=175	
	ULTOMIRIS (n=86) n (%)	Placebo (n=89) n (%)
Gastrointestinal disorders		
Diarrhoea	13 (15)	11 (12)
Abdominal pain	5 (6)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	12 (14)	7 (8)
Urinary tract infection	5 (6)	4 (4)
Musculoskeletal and connective tissue disorders		
Back pain	7 (8)	5 (6)
Nervous system disorders		
Dizziness	8 (9)	3 (3)

*Grouped term includes Nasopharyngitis, Oropharyngeal pain, Pharyngitis, and Upper respiratory tract infection.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

The safety of ULTOMIRIS has been evaluated in 58 adult patients with NMOSD who received at least one dose of ULTOMIRIS administered intravenously, including 55 patients who were exposed for at least 12 months, and 21 who were exposed for at least 18 months (see *section 5.1, Pharmacodynamic Properties, Clinical Trials, Neuromyelitis Optica Spectrum Disorder).* In Study ALXN1210-NMO-307, an open-label multicentre trial, the most frequent adverse reactions (≥10%) with ULTOMIRIS were headache, back pain, urinary tract infection and arthralgia. Table 14 describes adverse reactions that occurred at a rate of 5% or more in intravenous ULTOMIRIS-treated patients. Serious adverse reactions were reported in 8 (13.8%) patients with NMOSD receiving ULTOMIRIS.

Of these serious adverse reactions, one case of pneumonia, one case of intervertebral discitis, and two cases of meningococcal infections were reported in patients treated with ULTOMIRIS. Both patients with meningococcal infections were treated promptly and recovered with no sequelae.

Table 14 Adverse Events Reported in ≥ 5% in ULTOMIRIS Treated Adult Patients with NMOSD in Study ALXN1210-NMO-307

Body System Adverse Event	**N=58** **n (%)**
Blood and Lymphatic System Disorder	
Lymphadenopathy	3 (5.2)
Gastrointestinal Disorders	
Constipation	4 (6.9)
Vomiting	4 (6.9)
Diarrhoea	3 (5.2)
Gastrooesophageal reflux disease	3 (5.2)
General Disorders and Administration Site Reactions	
Pyrexia	5 (8.6)
Chills	3 (5.2)
Fatigue	3 (5.2)
Malaise	3 (5.2)
Non-cardiac chest pain	3 (5.2)
Vaccination site pain	3 (5.2)
Infections and Infestations	
COVID-19*	14 (24.1)
Urinary tract infection	6 (10.3)
Cystitis	5 (8.6)
Upper respiratory tract infection	5 (8.6)
Nasopharyngitis	3 (5.2)
Sinusitis	3 (5.2)
Injury, Poisoning and Procedural Complications	
Infusion related reaction	4 (6.9)
Musculoskeletal and Connective Tissue Disorders	
Back pain	7 (12.1)
Arthralgia	6 (10.3)
Myalgia	3 (5.2)
Nervous System Disorders	
Headache	14 (24.1)
Dizziness	4 (6.9)
Migraine	3 (5.2)
Respiratory, thoracic and mediastinal disorders	
Cough	3 (5.2)

*Nearly all participants were enrolled in Study ALXN1210-NMO-307 during the COVID-19 pandemic. No study participants died due to COVID-19 and the reported adverse events were not serious and did not result in treatment discontinuation.

Description of selected adverse reactions

In clinical studies, the most serious adverse reaction from ULTOMIRIS was meningococcal infection/sepsis (see *section 4.4 Special Warnings and Precautions for Use*). Meningococcal infections in patients treated with ULTOMIRIS have presented as meningococcal sepsis and encephalitis meningococcal. Patients should be informed of the signs and symptoms of meningococcal infection and advised to seek medical care immediately.

Post-marketing Experience

Infusion reactions

Administration of ULTOMIRIS may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In case of infusion reaction, infusion of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

Urticaria

Urticaria has been noted as a common adverse event in patients treated with ULTOMIRIS.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported to date.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Ravulizumab *rch* is a humanised monoclonal antibody (mAb) consisting of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148kDa. The constant regions of ravulizumab *rch* include the human kappa light chain constant region, and the protein engineered "IgG2/4" heavy chain constant region.

The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region (common to both human IgG2 and IgG4 amino acid sequences), while the remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

Mechanism of Action

Ravulizumab *rch* is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the pro-inflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9, also known as the membrane attack complex (MAC)]), thus preventing MAC formation. By binding specifically to C5, ravulizumab *rch* antagonises terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

This mechanism of action provides the therapeutic rationale for the use of ravulizumab *rch* in PNH, aHUS, gMG and NMOSD, in which uncontrolled complement activation is involved. In

patients with PNH, complement-mediated intravascular haemolysis is blocked with ravulizumab *rch* treatment. Ravulizumab *rch* also resolves the complement-mediated TMA present in aHUS. In patients with gMG, ravulizumab *rch* inhibits terminal complement activation which otherwise leads to MAC deposition at the neuromuscular junction resulting in impairment of neuromuscular transmission. In NMOSD, ravulizumab *rch* inhibits C5a dependant inflammation and MAC formation that otherwise leads to astrocytopathy and damage to surrounding glial cells and neurons.

Ravulizumab *rch* was specifically engineered to dissociate from C5 and associate with human neonatal Fc receptor (FcRn) at pH 6.0 (while minimising the impact in binding to C5 in intravascular space where the normal pH is 7.4). As a result, dissociation of antibody:C5 complexes in the acidified environment of the early endosome after pinocytosis is increased. Therefore, free antibody is recycled from the early endosome back into the vascular compartment by FcRn, resulting in an extended ravulizumab *rch* terminal elimination half-life (see *section 5.2 Pharmacokinetic Properties*).

Ravulizumab *rch* dosing has been optimised to achieve therapeutic steady state concentrations following the first dose, resulting in immediate onset of action and complete terminal complement inhibition by the end of infusion; ravulizumab *rch* half-life in serum yields prolonged pharmacologic activity, allowing dosing once every 8 weeks (or once every 4 weeks for patients weighing less than 20 kg).

Pharmacodynamic Effects

Following ravulizumab *rch* treatment in both adult and paediatric complement-inhibitor naïve patients and eculizumab *rmc*-experienced patients with PNH in Phase 3 studies, immediate and complete inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period (Figure 1 and Figure 2). In contrast, serum free C5 concentrations did not consistently remain < 0.5 µg/mL following eculizumab *rmc* treatment (Figure 1 and Figure 2).

Figure 1: Free C5 vs Time Profiles in Complement-Inhibitor Naïve Patients with PNH

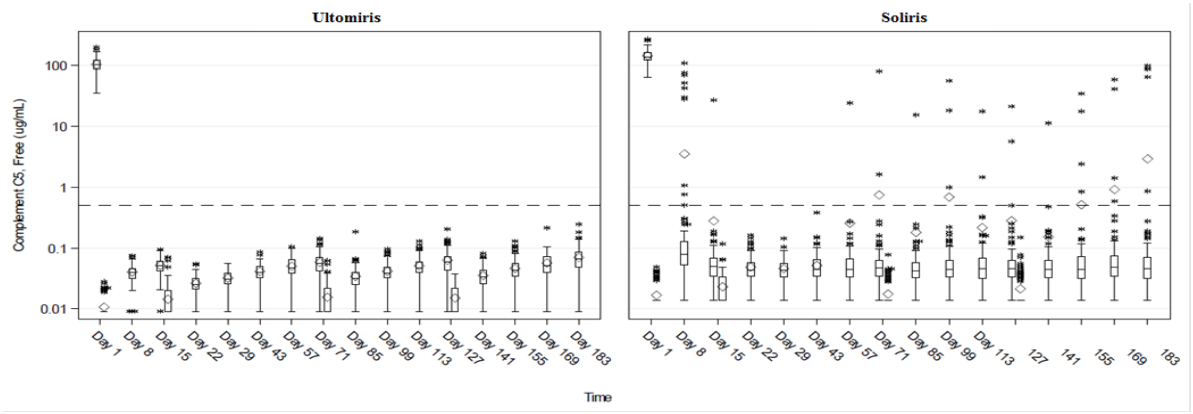
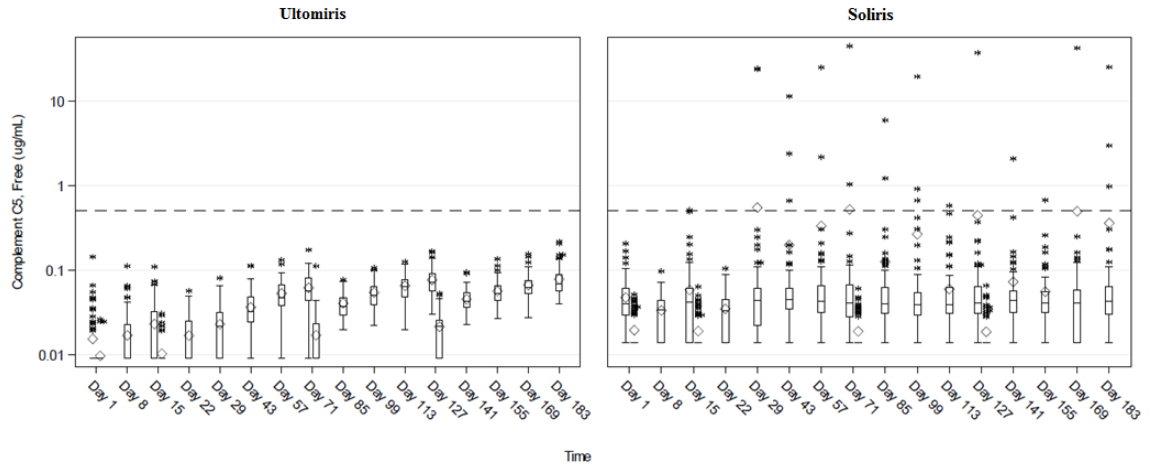


Figure 2: Free C5 vs Time Profiles in Eculizumab-Experienced Patients with PNH



Free C5 levels of <0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Following ravulizumab *rch* treatment administration, immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS, and adult patients with gMG and NMOSD by the end of the first infusion and was sustained throughout the primary treatment period.

The extent and duration of the pharmacodynamic response were exposure-dependent in patients with PNH, aHUS, gMG and NMOSD following ravulizumab *rch* treatment.

Clinical trials

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The clinical development program was designed to determine whether ULTOMIRIS is non-inferior to the current standard of care therapy, SOLIRIS (eculizumab *rmc*) in adult patients with PNH regardless of previous treatment status while assessing potential beneficial effects of a longer dosing interval. The safety and efficacy of ULTOMIRIS in patients with PNH were assessed in 2 distinct and complementary populations: a complement-inhibitor-naïve population of patients with active haemolysis to establish the magnitude of the efficacy response, and a population of patients stable on SOLIRIS therapy that allowed the assessment of the maintenance of efficacy and safety in a population switching to ULTOMIRIS.

Accordingly, 2 adequate and well controlled Phase 3 trials were conducted to cover each population:

- a Complement-Inhibitor Naïve Study in adult patients with PNH who were naïve to complement inhibitor treatment (ALXN1210-PNH-301),
- a SOLIRIS-experienced Study in patients with PNH who were clinically stable after having been treated with SOLIRIS (eculizumab *rmc*) for at least the previous 6 months (ALXN1210-PNH-302).

ULTOMIRIS was dosed in accordance with the recommended dosing described in *section 4.2 Dose and Method of Administration* (4 infusions of ULTOMIRIS over 26 weeks) while SOLIRIS was administered according to the approved dosing regimen of SOLIRIS (15 infusions over 26 weeks) which was the standard-of-care for PNH at the time of studies.

Patients were vaccinated against meningococcal infection prior to, or at the time of initiating treatment with ULTOMIRIS or SOLIRIS or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

There were no noteworthy differences in the demographic or baseline characteristics between the ULTOMIRIS and SOLIRIS treatment groups in either of the Phase 3 studies. Twelve-month transfusion history was similar between ULTOMIRIS and SOLIRIS treatment groups within each of the Phase 3 studies.

ALXN1210-PNH-301 Study in complement-inhibitor naïve adult patients with PNH.

The Complement-Inhibitor Naïve Study was a 26-week, multicentre, open-label, randomised, active-controlled, Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry and was followed by a long-term extension period where all patients received ULTOMIRIS.

PNH medical history was similar between ULTOMIRIS and SOLIRIS treatment groups. The 12-month transfusion history was similar between ULTOMIRIS and SOLIRIS treatment groups. More than 80% of patients in both treatment groups had a history of transfusion within 12 months of study entry. The majority of the Complement-Inhibitor Naïve Study population was highly haemolytic at baseline; 86.2% of enrolled patients presented with elevated LDH ≥ 3 x ULN, which is a direct measurement of intravascular haemolysis, in the setting of PNH. The median total red blood cell (RBC) clone size was 33.75%, consistent with ongoing active haemolysis of PNH erythrocytes in a patient population with a large median granulocyte clone size (92.55%).

Table 15 presents the baseline characteristics of the patients with PNH enrolled in the Complement-Inhibitor Naïve Study.

Table 15 Baseline Characteristics in the Complement-Inhibitor Naïve Study

Parameter	**Statistics**	**ULTOMIRIS (N = 125)**	**SOLIRIS (N = 121)**
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	37.9 (14.90) 34.0 15, 81	39.6 (16.65) 36.5 13, 82
Age (years) at first infusion in study	Mean (SD) Median Min, max	44.8 (15.16) 43.0 18, 83	46.2 (16.24) 45.0 18, 86
Sex (n, %)	Male Female	65 (52.0) 60 (48.0)	69 (57.0) 52 (43.0)
Pre-treatment LDH levels	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0
Number of patients with packed red blood cells (pRBC)/whole blood transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
pRBC/whole blood transfusions within 12 months prior to first dose	Total Mean (SD) Median	677 6.6 (6.04) 4.0	572 5.7 (5.53) 3.0
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0

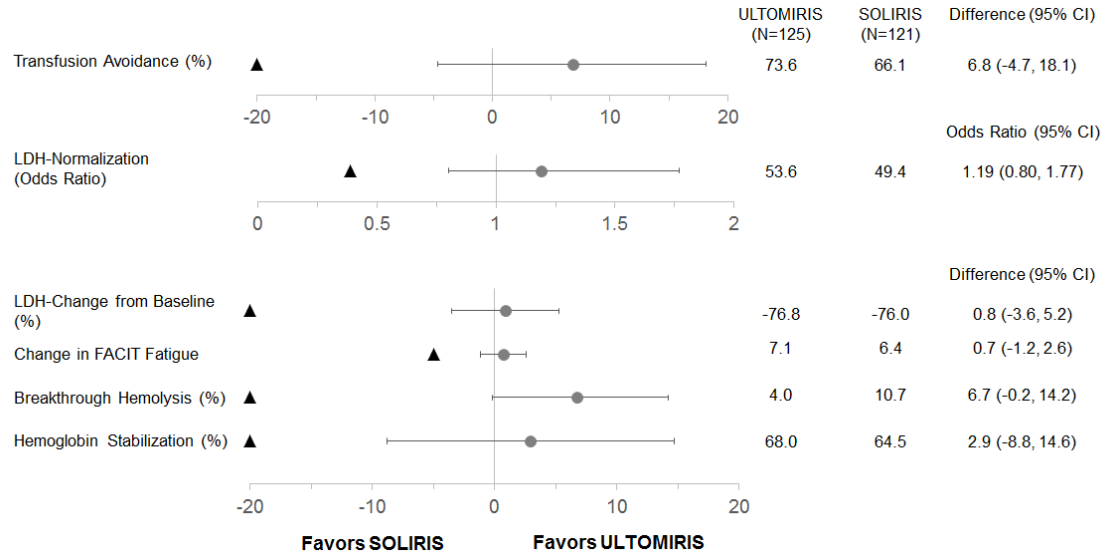
Parameter	Statistics	ULTOMIRIS (N = 125)	SOLIRIS (N = 121)
Patients with any PNH conditions prior to informed consent	n (%)	121 (96.8)	120 (99.2)
Anaemia		103 (82.4)	105 (86.8)
Haematuria or haemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anaemia		41 (32.8)	38 (31.4)
Renal failure		19 (15.2)	11 (9.1)
Myelodysplastic syndrome		7 (5.6)	6 (5.0)
Pregnancy complication		3 (2.4)	4 (3.3)
Other[a]		27 (21.6)	13 (10.7)

[a] "Other" as specified on case report form included thrombocytopenia, chronic kidney disease, and pancytopenia, as well as a number of other conditions.

The co-primary endpoints were transfusion avoidance and haemolysis as directly measured by normalisation of LDH levels. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion from baseline to Day 183. Key secondary endpoints included the percent change from baseline in LDH levels, change in quality of life (FACIT-Fatigue), the proportion of patients with breakthrough haemolysis and proportion of patients with stabilised haemoglobin.

In the Complement-Inhibitor Naïve Study, both co-primary endpoints, avoidance of packed red blood cells (pRBC) transfusion per protocol-specified guidelines, and LDH normalisation from Day 29 to Day 183, met the primary objective and showed ULTOMIRIS was statistically significant for non-inferiority compared to SOLIRIS. ULTOMIRIS also achieved statistically significant non-inferiority compared to SOLIRIS for all 4 key secondary endpoints. Both co-primary endpoints and all key secondary endpoints favoured ULTOMIRIS (Figure 3).

Figure 3: Analysis of Co-primary and Secondary Endpoints – Full Analysis Set (Complement-Inhibitor Naïve Study)



Note: The black triangle indicates the non-inferiority margins, and grey dots indicates point estimates
OR = Odds Ratio, FACIT = Functional Assessment of Chronic Illness Therapy

Transfusion avoidance through Day 183 was achieved by 73.6% of patients in the ULTOMIRIS group compared to 66.1% in the SOLIRIS group. The difference between the ULTOMIRIS and SOLIRIS treatment groups in the percentage of patients who avoided transfusion was 6.8% (95% CI: -4.66%, 18.14%). The total number of units transfused was also lower for the ULTOMIRIS

group (222 for SOLIRIS vs 155 for ULTOMIRIS). The adjusted prevalence of LDH normalisation (LDH levels ≤ 1 × ULN (upper limit of normal) from Day 29 through Day 183) was 53.6% for the ULTOMIRIS group and 49.4% for the SOLIRIS group. The adjusted odds ratio for LDH normalisation for the comparison of ULTOMIRIS to SOLIRIS was 1.187 (95% CI: 0.796, 1.769). The median time to first LDH normalisation was 24 days for ULTOMIRIS and 29 days for SOLIRIS.

The mean percent change in LDH from baseline to Day 183 was -76.84% for the ULTOMIRIS group and -76.02% for the SOLIRIS group. The mean difference between treatment groups was -0.83% (95% CI: -5.21%, 3.56%).

The mean change in FACIT-Fatigue total score from baseline to Day 183 was 7.07 for the ULTOMIRIS group and 6.40 for the SOLIRIS group, with a 3-point improvement from baseline on this scale considered a clinically meaningful improvement. The mean difference between treatment groups was 0.67 (95% CI: -1.21, 2.55). Both treatment groups showed improvement in fatigue as measured by FACIT-Fatigue overtime. Improvement was numerically greater with ULTOMIRIS than SOLIRIS at all time points for FACIT-Fatigue.

Breakthrough haemolysis defined as at least 1 new or worsening symptom or sign of intravascular haemolysis in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy, was experienced by 4.0% of patients in the ULTOMIRIS group and 10.7% of patients in the SOLIRIS group. The difference between treatment groups was -6.7% (95% CI: -14.21%, 0.18%).

Haemoglobin stabilisation defined as an avoidance of a ≥2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 was achieved by 68.0% of patients in the ULTOMIRIS group and 64.5% of patients in the SOLIRIS group. The difference between treatment groups was 2.9% (95% CI: -8.80%, 14.64%).

Because statistically significant non-inferiority was achieved for both co-primary and all 4 key secondary endpoints, superiority was assessed following the pre-specified hierarchical testing order that began with the breakthrough haemolysis endpoint. The treatment difference for breakthrough haemolysis ($p = 0.0558$) did not reach the pre-specified threshold for superiority ($p < 0.05$), and no further testing was conducted. The incidence of breakthrough haemolysis was more than 2-fold higher in the SOLIRIS group (13 patients with 15 events) than in the ULTOMIRIS group (5 patients with 5 events). Of the 15 breakthrough haemolysis events seen in the SOLIRIS group, 7 were associated with elevated free C5 above 0.5 µg/mL. No patients in the ULTOMIRIS group had elevations of free C5 levels above 0.5 µg/mL.

The final efficacy analysis for the study included all patients ever treated with ULTOMIRIS (n=244) and had a median treatment duration of 203.3 weeks (1423 days). The final analysis confirmed that ULTOMIRIS treatment responses observed during the Primary Evaluation Period (through week 26) were maintained throughout the duration of the study.

<u>ALXN1210-PNH-302 Study in adult PNH patients previously treated with SOLIRIS</u>

The SOLIRIS-Experienced Study was a 26-week, multicentre, open-label, randomised, active-controlled Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with SOLIRIS (eculizumab *rmc*) for at least the past 6 months and was followed by a long-term extension period where all patients received ULTOMIRIS.

PNH medical history was similar between ULTOMIRIS and SOLIRIS treatment groups. The 12-month transfusion history was similar between ULTOMIRIS and SOLIRIS treatment groups and

more than 87% of patients in both treatment groups had not received a transfusion within 12 months of study entry. Per study entry criteria, all patients presented with controlled haemolysis at baseline, consistent with a population under continuous treatment with SOLIRIS. The mean total PNH RBC clone size was 60.05%, the mean total PNH granulocyte clone size was 83.30%, and the mean total PNH monocyte clone size was 85.86%.

Table 16 presents the baseline characteristics of the PNH patients enrolled in the SOLIRIS-experienced Study.

Table 16 Baseline Characteristics in the SOLIRIS-Experienced Study

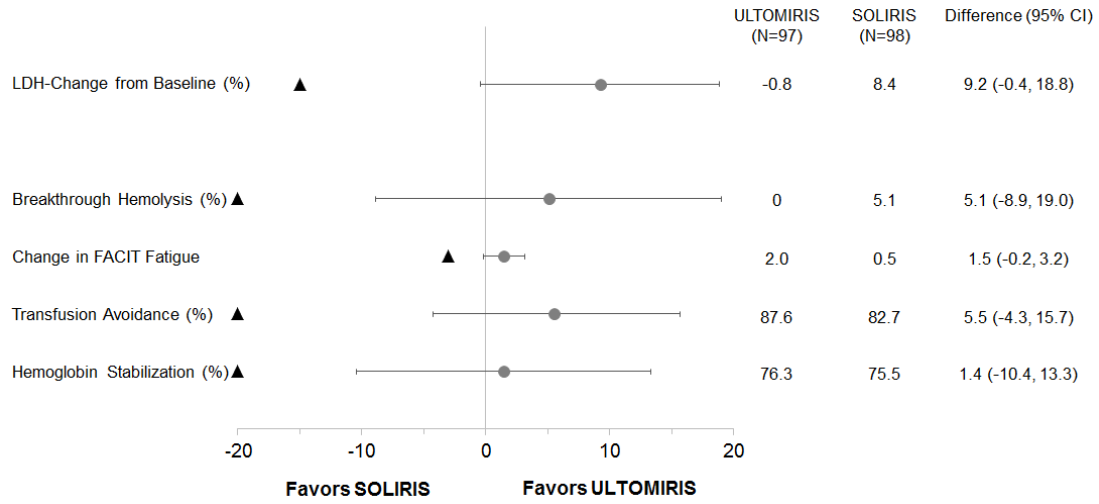
Parameter	Statistics	ULTOMIRIS (n = 97)	SOLIRIS (n = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	50 (51.5) 47 (48.5)	48 (49.0) 50 (51.0)
Pre-treatment LDH levels	Mean (SD) Median	228.0 (48.71) 224.0	235.2 (49.71) 234.0
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose	n (%)	13 (13.4)	12 (12.2)
pRBC/whole blood transfusions within 12 months prior to first dose	Total Mean (SD) Median	64 4.9 (5.51) 3.0	30 2.5 (2.32) 1.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	103 7.9 (8.78) 4.0	50 4.2 (3.83) 2.5
Patients with any PNH conditions prior to informed consent	n (%)	90 (92.8)	96 (98.0)
Anaemia		64 (66.0)	67 (68.4)
Haematuria or haemoglobinuria		47 (48.5)	48 (49.0)
Aplastic anaemia		34 (35.1)	39 (39.8)
Renal failure		11 (11.3)	7 (7.1)
Myelodysplastic syndrome		3 (3.1)	6 (6.1)
Pregnancy complication		4 (4.1)	9 (9.2)
Other[a]		14 (14.4)	14 (14.3)

[a] "Other" category included neutropenia, renal dysfunction, and thrombocytopenia, as well as a number of other conditions.

The primary endpoint was haemolysis as measured by LDH percent change from baseline. Secondary endpoints included the proportion of patients with breakthrough haemolysis, quality-of-life (FACIT-Fatigue), transfusion avoidance, and proportion of patients with stabilised haemoglobin.

In the SOLIRIS-Experienced Study, the primary endpoint, Percent Change in LDH from baseline to Day 183, met the primary objective and showed ULTOMIRIS was statistically significant for non-inferiority compared to SOLIRIS. ULTOMIRIS also achieved statistically significant non-inferiority compared to SOLIRIS for all 4 key secondary endpoints. Both the primary endpoints and all key secondary endpoints favoured ULTOMIRIS (Figure 4).

Figure 4 Analysis of Primary and Secondary Endpoints – Full Analysis Set (SOLIRIS Experienced Study)



Note: The black triangle indicates the non-inferiority margins, and grey dot indicates point estimates.
FACIT = Functional Assessment of Chronic Illness Therapy

Mean percent change in LDH from baseline to Day 183 showed a decrease of less than 1% (-0.82%) for the ULTOMIRIS group and an increase of greater than 8% (+8.39%) for the SOLIRIS group with a treatment difference (ULTOMIRIS-SOLIRIS) of -9.21% (95% CI: -18.84%, 0.42%).

Breakthrough haemolysis, using the same definition as the Complement-Inhibitor Naïve Study, was experienced by none of the patients in the ULTOMIRIS group and 5 (5.1%) of the patients in the SOLIRIS group. The difference between treatment groups was -5.1% (95% CI: -18.99%, 8.89%). The incidence of breakthrough haemolysis was higher in the SOLIRIS group (7 events) than in the ULTOMIRIS group (0 events). Of the 7 breakthrough haemolysis events seen in the SOLIRIS group, 4 were associated with elevated free C5 above 0.5 µg/mL. There were no breakthrough haemolysis events in the ULTOMIRIS group and no patients in the ULTOMIRIS group had elevations of free C5 levels above 0.5 µg/mL.

The mean change in the FACIT-Fatigue total score from baseline to Day 183 was 2.01 for the ULTOMIRIS group and 0.54 for the SOLIRIS group. The LS mean difference between treatment groups was 1.5 (95% CI: -0.2, 3.2). Both treatment groups showed improvement in fatigue as measured by FACIT-Fatigue over time; improvement was numerically greater with ULTOMIRIS than SOLIRIS at all time points for the FACIT-fatigue following Day 8.

Transfusion avoidance was achieved by 87.6% of patients on ULTOMIRIS compared to 82.7% of patients on SOLIRIS by Week 26. The difference between the ULTOMIRIS and SOLIRIS treatment groups in the percentage of patients who avoided transfusion was 5.5% (95% CI: -4.27%, 15.68%).

Haemoglobin stabilisation through Day 183 was achieved by 76.3% of patients in the ULTOMIRIS group and 75.5% of patients in the SOLIRIS group. The difference between treatment groups was 1.4% (95% CI: -10.41%, 13.31%).

As statistically significant non-inferiority was achieved for the primary endpoint and all 4 key secondary endpoints, the pre-specified hierarchical order continued with superiority testing of percent change from baseline in LDH. The assessment of the treatment difference for superiority

resulted in a p-value of 0.0583 which did not reach the pre-specified significance threshold for superiority ($p < 0.05$) and therefore no additional testing in the hierarchy was conducted.

Overall, treatment with ULTOMIRIS in both complement-inhibitor naïve and SOLIRIS-experienced patients was associated with clinically meaningful benefits across disease-relevant endpoints and reduction of the overall risk of breakthrough haemolysis through better C5 control and elimination of the risk of pharmacodynamic-associated breakthrough haemolysis.

The final efficacy analysis for the study included all patients ever treated with ULTOMIRIS (n=192) and had a median treatment duration of 138.3 weeks (968 days). The final analysis confirmed that ULTOMIRIS treatment responses observed during the Primary Evaluation Period (through week 26) were maintained throughout the duration of the study.

ALXN1210-PNH-304 Study in paediatric patients with PNH

The paediatric study was a multi-centre, open-label, Phase 3 study conducted in SOLIRIS-experienced and complement inhibitor treatment naïve paediatric patients with PNH. Patients who completed the 26-week Primary Evaluation Period were followed for up to 4 years in the long-term Extension Period.

A total of 13 PNH paediatric patients completed ULTOMIRIS treatment during the Primary Evaluation Period (26 weeks) of Study ALXN1210-PNH-304. Five of the 13 patients had never been treated with complement inhibitors and 8 patients were treated with SOLIRIS (eculizumab *rmc*). Eleven of the 13 patients were between 12 and 17 years of age at first infusion, with 2 patients under 12 years old (11 and 9 years old). Based on body weight, patients received a loading dose of ULTOMIRIS on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on SOLIRIS therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of SOLIRIS.

Table 17 presents the baseline characteristics of the PNH patients enrolled in the Paediatric PNH Study.

Table 17 Demographics and Baseline Characteristics - Full Analysis Set

Variable	**Treatment-Naïve (N = 5)**	**SOLIRIS-Experienced (N = 8)**
Sex, n (%)		
Male	4 (80.0)	1 (12.5)
Female	1 (20.0)	7 (87.5)
Race, n (%)		
White	5 (100)	3 (37.5)
Black or African American	0 (0.0)	2 (25.0)
Not Reported	0 (0.0)	2 (25.0)
Other	0 (0.0)	1 (12.5)
Age at first infusion (years)		
Mean (SD)	14.4 (2.19)	14.4 (3.07)
Median (min, max)	15.0 (11, 17)	15.0 (9, 17)
Age at first infusion (years) category, n (%)		
< 12 years	1 (20.0)	1 (12.5)
≥ 12 years	4 (80.0)	7 (87.5)

Variable	Treatment-Naïve (N = 5)	SOLIRIS-Experienced (N = 8)
Baseline Weight (kg)		
Mean (SD)	56.26 (11.594)	56.25 (12.247)
Median (min, max)	55.60 (39.5, 72.0)	55.50 (36.7, 69.0)
Baseline weight (kg), n (%)		
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)
Pre-treatment LDH levels (U/L)		
Median (min, max)	588.50 (444, 2269.7)	251.50 (140.5, 487)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	2 (40.0)	2 (25.0)
Number of pRBC/whole blood transfusions within 12 months prior to first dose		
Total	10	2
Median (min, max)	5.0 (4, 6)	1.0 (1, 1)
Units of pRBC/whole blood transfused within 12 months prior to first dose		
Total	14	2
Median (min, max)	7.0 (3, 11)	2.0 (2, 2)
Patients with any PNH-associated conditions prior to informed consent, n (%)	5 (100)	8 (100)
Anaemia	2 (40.0)	5 (62.5)
Haematuria or haemoglobinuria	2 (40.0)	5 (62.5)
Aplastic anaemia	3 (60.0)	1 (12.5)
Renal failure	2 (40.0)	2 (25.0)
Other[a]	0	1 (12.5)

[a] Other PNH-associated conditions were reported as "renal and splenic infarcts" and "multiple lesions concerning for embolic process".

Note: Percentages were based on the total number of patients in each cohort, or overall.

Abbreviations: max = maximum; min = minimum; SD = standard deviation

The weight-based dose regimen of ULTOMIRIS provided immediate, complete, and sustained inhibition of terminal complement throughout the 26-week Primary Evaluation Period, regardless of prior experience with SOLIRIS. Following initiation of ULTOMIRIS treatment, steady-state therapeutic serum concentrations of ULTOMIRIS were achieved immediately after the first dose and maintained throughout the Primary Evaluation Period in both cohorts. There were no breakthrough haemolysis events during the Primary Evaluation Period, and no patients had post-baseline free C5 levels above 0.5 µg/mL. Mean percent change from baseline in LDH was -47.91% on Day 183 in the complement inhibitor treatment naïve cohort and remained stable in the SOLIRIS-experienced cohort during the 26-week Primary Evaluation Period. Three (60%) of the 5 complement inhibitor treatment-naïve patients and 6 (75%) of the 8 SOLIRIS-experienced patients achieved haemoglobin stabilisation by Week 26, respectively. Transfusion-avoidance was reached for 85% (11/13) of patients during the 26-week Primary Evaluation Period.

Table 18 presents secondary efficacy outcomes for the Primary Evaluation Period.

Table 18 Secondary efficacy outcomes from the interim analysis of Paediatric study in PNH patients - 26-week Primary Evaluation Period

End Point	Treatment Naïve (n = 5)	SOLIRIS Experienced (n = 8)
LDH- percent change from baseline, Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion avoidance percentage (95% CI)	60.0 (14.66, 94.73)	100.0 (63.06, 100.00)
Haemoglobin stabilisation percentage (95% CI)	60.0 (14.66, 94.73)	75 (34.91, 96.81)
Breakthrough Haemolysis (%)	0	0

Abbreviations: LDH = lactate dehydrogenase

Efficacy results through end of study over a median treatment duration of 130.7 weeks (915 days) confirmed that ULTOMIRIS treatment responses observed during the Primary Evaluation Period (through week 26) were maintained throughout the duration of the study.

The efficacy of ULTOMIRIS in paediatric PNH patients appears to be similar to that observed in adult PNH patients enrolled in pivotal studies.

atypical Haemolytic Uraemic Syndrome (aHUS)

The safety and efficacy of ULTOMIRIS in patients with aHUS were assessed in 2 open label, single arm, Phase 3 studies. Study ALXN1210-aHUS-311 enrolled adult patients with aHUS and Study ALXN1210-aHUS-312 enrolled paediatric patients with aHUS.

ALXN1210-aHUS-311 Study in adult patients with aHUS

The adult study was a multicentre, single arm, Phase 3 study conducted in patients who were naïve to complement inhibitor treatment prior to study entry and had evidence of TMA. The study consisted of a 26-week Initial Evaluation Period and patients were allowed to enter an Extension Period for up to 4.5 years.

A total of 58 patients with documented aHUS were enrolled. Enrolment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, STEC-HUS and genetic defect in cobalamin C metabolism. Two patients were excluded from the Full Analysis Set due to a confirmed diagnosis of STEC-HUS. The majority of patients (92.9%) had extra renal signs or symptoms of aHUS at baseline. At baseline, 72.2% (n = 39) of patients had Stage 5 chronic kidney disease (CKD).

Table 19 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 19 Baseline Characteristics in the Adult aHUS Study

Parameter	Statistics	ULTOMIRIS (n = 56)
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male Female	n (%)	 19 (33.9) 37 (66.1)

Parameter	Statistics	ULTOMIRIS (n = 56)
Race [a]		
Asian	n (%)	15 (26.8)
White		29 (51.8)
Unknown		8 (14.3)
Other		4 (7.2)
Any pre-treatment extra-renal signs or symptoms of aHUS	n (%)	52 (92.9)
Cardiovascular		39 (69.6)
Pulmonary		25 (44.6)
Central nervous system		29 (51.8)
Gastrointestinal		35 (62.5)
Skin		17 (30.4)
Skeletal muscle		13 (23.2)
History of transplant	n (%)	8 (14.3)
Patients post partum	n (%)	8 (14.3)
Platelets (10^9/L) blood [normal range 130 to 400 × 10^9/L]	n Mean (SD) Median (min,max)	56 118.52 (86.440) 95.25 (18, 473)
Haemoglobin (g/L) blood [normal range 115 to 160 g/L (female), 130 to 175 g/L (male)]	n Mean (SD) Median (min,max)	56 86.26 (14.866) 85.00 (60.5, 140)
LDH (U/L) serum [normal range 120 to 246 U/L]	n Mean (SD) Median (min,max)	56 702.38 (557.959) 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	n (%) Mean (SD) Median (min,max)	55 15.86 (14.815) 10.00 (4, 80)
Patients on dialysis	n (%)	29 (51.8)

Note: Percentages are based on the total number of patients.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. For patients on dialysis at baseline, the first valid creatinine value used as the baseline value was the first assessment ≥ 6 days post dialysis.

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week Initial Evaluation Period as shown in Table 20.

Table 20 Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	56	30	0.536 (0.396, 0.675)
Components of Complete TMA Response			
Platelet count normalisation	56	47	0.839 (0.734, 0.944)
LDH normalisation	56	43	0.768 (0.648, 0.887)
≥25% improvement in serum creatinine from baseline	56	33	0.589 (0.452, 0.727)
Haematologic normalisation	56	41	0.732 (0.607, 0.857)

[a]95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Complete TMA Response was observed in six additional patients during the Extension Period (at Days 169, 302, 401, 407, 1247 and 1359) resulting in an overall Complete TMA Response in 36 of 56 patients (64.3%; 95% CI: 50.8%, 77.7%) through end of study. Individual component response increased to 48 (85.7%; 95% CI: 75.7%, 95.8%) patients for platelet count normalisation, 49 (87.5%; 95% CI: 77.9%, 97.1%) patients for LDH normalisation, and 37 (66.1%; 95% CI: 52.8%, 79.4%) patients for renal function improvement.

The median time to Complete TMA Response was 86 days (7 to 1359 days). A rapid increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 243.54 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). Similarly, the mean LDH value decreased from baseline over the first 2 months of treatment and was sustained over the duration of the Initial Evaluation Period (26 weeks). Table 21 summarises the secondary efficacy results for Study ALXN1210-aHUS-311.

Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS treatment. By Day 743 of the study, over two thirds of the remaining patient population (26/36), who were mostly CKD Stage 4 or 5 at baseline, improved their CKD stages. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week Initial Evaluation Period. Eighteen of the 25 patients who required dialysis at study entry were able to discontinue dialysis by the end of the Initial Evaluation Period, with 2 additional patients discontinuing dialysis during the Extension Period. While 8 participants who were off dialysis at baseline-initiated dialysis during the study.

Table 21 Secondary Efficacy Outcomes for Study in Adult Patients with aHUS

Parameters	N = 56	
Haematologic TMA parameters, Day 183	Observed value (n=48)	Change from baseline (n=48)
Platelets (10^9/L) blood		
Mean (SD)	237.96 (73.528)	114.79 (105.568)
Median	232.00	125.00
LDH (U/L) serum		
Mean (SD)	194.46 (58.099)	-519.83 (572.467)
Median	176.50	-310.75
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/n	40/56	
proportion (95% CI)**	0.71 (0.59, 0.84)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	32/47	
Proportion (95% CI)*	0.68 (0.53, 0.81)	
Worsened[b]		
m/n	2/13	
Proportion (95% CI)*	0.15 (0.02, 0.45)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=48)	Change from baseline (n=47)
Mean (SD)	51.83 (39.16)	34.80 (35.45)
Median	40.00	29.00

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 5 is considered the worst category, while Stage 1 is considered the best category. Baseline is derived based on the last available eGFR before starting treatment. Improved/Worsened: Compared to CKD stage at baseline. [a]Improved: Excluded those with Stage 1 at baseline as they cannot improve. [b]Excludes patients with Stage 5 at baseline as they cannot worsen. *95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper-Pearson method. **95% confidence intervals (95% CIs) for the proportion are based on the asymptotic Gaussian approximation method with a continuity correction.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

The final efficacy analysis for the study on all patients treated with ULTOMIRIS over a median treatment duration 130.4 weeks confirmed that treatment responses observed during the Primary Evaluation Period (through week 26) were maintained throughout the duration of the study.

ALXN1210-aHUS-312 Study in paediatric patients with aHUS

Study ALXN1210-aHUS-312 was a 26-week, multicentre, single arm, Phase 3 study conducted in paediatric patients. After the 26-week Initial Evaluation Period, patients were allowed to enter an Extension Period for up to 4.5 years.

A total of 24 SOLIRIS-naïve patients with documented diagnosis of aHUS and evidence of TMA were enrolled, of whom 20 were included in the Full Analysis Set. The median age at the time of first infusion was 4.8 years (range: 0.9, 17.3 years). Enrolment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, STEC-HUS and genetic defect in cobalamin C metabolism. Four patients were given 1 or 2 doses but were excluded from the study because eligibility criteria were not confirmed for aHUS diagnosis.

The overall mean weight at baseline was 21.2 kg; the majority of patients (55%) were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (70.0%) had pre-treatment extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 35.0% (n = 7) of patients had CKD Stage 5.

A total of 10 patients who switched from SOLIRIS to ULTOMIRIS with documented diagnosis of aHUS were enrolled. Patients had to have a clinical response to SOLIRIS prior to enrolment i.e. LDH < 1.5 x ULN and platelet count ≥ 150,000/µL, and eGFR > 30 mL/min/1.73m^2). Consequently, there is no information on the use of ULTOMIRIS in patients refractory to SOLIRIS.

Table 22 presents the baseline characteristics of the paediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 22 Demographics and Baseline Characteristics in Paediatric Study in Patients with aHUS

Parameter	Statistics	ULTOMIRIS Naïve (n = 20)	ULTOMIRIS Switch (n = 10)
Age at time of first infusion (years) category			
Birth to < 2 years	n (%)	4 (20.0)	1 (10.0)
2 to < 6 years		9 (45.0)	1 (10.0)
6 to < 12 years		5 (25.0)	1 (10.0)
12 to < 18 years		2 (10.0)	7 (70.0)
Sex			
Male	n (%)	8 (40.0)	9 (90.0)
Female		12 (60.0)	1 (10.0)
Race[a]			
Asian	n (%)	5 (25.0)	4 (40.0)
Black or African American		3 (15.0)	1 (10.0)
White		11 (55.0)	5 (50.0)
Unknown		1 (5.0)	0 (0.0)
Other		1 (5.0)	0 (0.0)
Any pre-treatment extra-renal signs or symptoms of aHUS	n (%)	14 (70.0)	1 (10.0)
Cardiovascular		9 (45.0)	1 (10.0)
Pulmonary		1 (5.0)	0 (0.0)
Central Nervous System		7 (35.0)	0 (0.0)
Gastrointestinal		12 (60.0)	0 (0.0)
Skin		10 (50.0)	0 (0.0)
Skeletal muscle		1 (5.0)	0 (0.0)
History of transplant	n (%)	1 (5.0)	1 (10.0)
Platelets (10^9/L) blood [normal range 229 to 533 × 10^9/L]	Mean (SD)	71.70 (49.32)	287.9 (74.59)
	Median (min, max)	64.0 (14, 224)	281.8 (207, 415.5)
Haemoglobin (g/L) blood [normal range 107 to 131 g/L]	Mean (SD)	74.93 (17.18)	131.5 (11.31)
	Median (min, max)	74.25 (32, 106)	132.0 (114.5, 148)
LDH (U/L) serum [normal range 165 to 395 U/L]	Mean (SD)	2141.21 (1275.26)	219.4 (56.85)
	Median (min, max)	1799.0 (772, 4985)	206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	Mean (SD)	27.5 (22.10)	104.9 (29.55)
	Median (min, max)	22.0 (10, 84)	99.8 (54, 136.5)
Required dialysis at baseline	n (%)	7 (35.0)	0 (0.0)

Note: Percentages are based on the total number of patients.

[a] Patients can have multiple races selected.

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline in SOLIRIS-naïve patients. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 15 of the 20 naïve patients (75.0%) during the 26-week Initial Evaluation Period as shown in Table 23.

Table 23 Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period

	Total	Responder	
		N	Proportion (95% CI)[a]
Complete TMA Response	20	15	0.750 (0.509, 0.913)
Components of Complete TMA Response			
Platelet count normalisation	20	19	0.950 (0.751, 0.999)
LDH normalisation	20	18	0.900 (0.683, 0.988)
≥25% improvement in serum creatinine from baseline	20	16	0.800 (0.563, 0.943)
Haematologic normalisation	20	18	0.900 (0.683, 0.988)

Note: Four patients were given 1 or 2 doses but were excluded from the study because eligibility criteria were not confirmed for aHUS diagnosis.
[a] 95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range: 15 to 99 days). All patients with Complete TMA Response maintained it through the Initial Evaluation Period, with continuous improvements seen in renal function. A rapid increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 71.70 × 10^9/L at baseline to 302.41 × 10^9/L at Day 8 and remained above 304 × 10^9/L at all subsequent visits after Day 22 in the Initial Evaluation Period (26 weeks).

Complete TMA Response was observed in three additional patients during the Extension Period (2 patients on Day 295 and 1 patient on Day 351) resulting in the achievement of Complete TMA response in 18 of 20 paediatric patients (90.0%; 95% CI: 68.3%, 98.8%) through end of study. Individual component response increased to 19 of 20 (95.0%; 95% CI: 75.1%, 99.9%) patients each for platelet count normalisation, LDH normalisation, and in 18 of 20 (90.0%; 95% CI; 68.3%, 98.8%) patients for renal function improvement. The improvement noted in mean eGFR observed by Week 26 was sustained through the end of the study.

Table 24 summarises the secondary efficacy results for Study ALXN1210-aHUS-312.

All 7 patients who required dialysis at study entry were able to discontinue dialysis; 6 of which had already done so by Day 36. No patient started or re-initiated dialysis during the study. For the 16 patients with available baseline and Week 52 (Day 351) data, 16 patients had improvement in CKD stage compared with baseline. Patients with available data through the end of the study continued to have improvements or no changes in CKD stage.

Table 24 Secondary Efficacy Outcomes for Paediatric Study in Patients with aHUS

Parameters	N=20	
Haematologic TMA parameters, Day 183	Observed value (n=17)	Change from baseline (n=17)
Platelets (10^9/L) blood		
Mean (SD)	304.94 (75.711)	245.59 (91.827)
Median	318.00	247.00
LDH (U/L) serum		
Mean (SD)	262.41 (59.995)	-2044.13 (1328.059)
Median	247.00	-1851.50
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/N	17/20	
proportion (95% CI)*	0.850 (0.621, 0.968)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	15/17	
Proportion (95% CI)*	0.882 (0.636, 0.985)	
Worsened[b]		
m/n	0/11	
Proportion (95% CI)*	0.000 (0.000, 0.285)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=17)	Change from baseline (n=17)
Mean (SD)	108.5 (56.87)	85.4 (54.33)
Median	108.0	80.00

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 1 is considered the best category, while Stage 5 is considered the worst category. Baseline is derived based on the last available eGFR before starting treatment. Improved/Worsened: Compared to CKD stage at baseline.

[a] Improved: Excluded those with Stage 1 at baseline as they cannot improve. [b]Worsened: Excludes patients with Stage 5 at baseline as they cannot worsen.

*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper Pearson method.

Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

The efficacy of ULTOMIRIS for the treatment of aHUS appear similar in paediatric and adult patients. Efficacy results through end of study over a median treatment duration of 130.6 weeks confirmed that ULTOMIRIS treatment responses observed during the Primary Evaluation Period (through week 26) were maintained throughout the duration of the study.

In SOLIRIS-experienced patients, switching to ULTOMIRIS maintained disease control as evidenced by stable haematologic and renal parameters, with no apparent impact on safety.

Generalised Myasthenia Gravis (gMG)

The efficacy and safety of ULTOMIRIS in adult patients with gMG was assessed in a Phase 3, randomised, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306) designed to demonstrate ULTOMIRIS superiority over placebo. Patients participating in this study were randomised 1:1 to either receive ULTOMIRIS or placebo for the 26-week Randomised-Controlled Period (RCP), and were subsequently allowed to enter an Open-Label Extension (OLE) Period during which all patients received ULTOMIRIS.

Patients with gMG (diagnosed for at least 6 months) with a positive serologic test for anti-acetylcholine receptor (AChR) antibodies, MGFA (Myasthenia Gravis Foundation of America) clinical classification Class II to IV and Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 6 were randomised to receive either ULTOMIRIS (N = 86) or placebo (N = 89). Patients on immunosuppressant therapies (ISTs) (corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus) were permitted to continue on therapy throughout the course of the study. In addition, rescue therapy (including high-dose corticosteroid, PE/PP, or IVIg) was allowed if a patient experienced clinical deterioration, as defined by the study protocol.

A total of 162 (92.6%) patients completed the 26-week RCP of Study ALXN1210-MG-306. The baseline characteristics of patients were balanced across the 2 treatment groups (Table 25).

Table 25 Baseline Disease Characteristics in Study ALXN1210-MG-306

Parameter	**Statistics**	**Placebo (N = 89)**	**ULTOMIRIS (N = 86)**
Sex	n (%)		
Male		44 (49.4)	42 (48.8)
Female		45 (50.6)	44 (51.2)
Age at first dose of study drug (years)	Mean (SD)	53.3 (16.05)	58.0 (13.82)
	(min, max)	(20, 82)	(19, 79)
Duration of MG since diagnosis (years)	Mean (SD)	10.0 (8.90)	9.8 (9.68)
	(min, max)	(0.5, 36.1)	(0.5, 39.5)
	Median	7.6	5.7
Baseline MG-ADL Score	Mean (SD)	8.9 (2.30)	9.1 (2.62)
	(min, max)	(6.0, 15.0)	(6.0, 24.0)
	Median	9.0	9.0
Baseline QMG Score	Mean (SD)	14.5 (5.26)	14.8 (5.21)
	(min, max)	(2.0, 27.0)	(6.0, 39.0)
	Median	14.0	15.0
Baseline MGFA classification	n (%)		
Class II (mild weakness)		39 (44)	39 (45)
Class III (moderate weakness)		45 (51)	41 (48)
Class IV (severe weakness)		5 (6)	6 (7)
Any prior intubation since diagnosis (MGFA Class V)	n (%)	9 (10.1)	8 (9.3)
Number of patients with prior MG crisis since diagnosis[a]	n (%)	17 (19.1)	21 (24.4)
Number of stable ISTs[b] at study entry	n (%)		
0		8 (9.0)	10 (11.6)
1		34 (38.2)	40 (46.5)
2+		47 (52.8)	36 (41.9)
Number of patients receiving stable corticosteroids at study entry	n (%)	65 (73.0)	56 (65.1)
Number of patients receiving other stable immunosuppressant agents[c] at study entry	n (%)	63 (70.8)	56 (65.1)

[a] Prior MG crisis information was collected as part of medical history and not evaluated as per the clinical protocol definition.
[b] Immunosuppressant therapies (ISTs) include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus.
[c] Other immunosuppressant agents include azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus.
Abbreviations: Max = maximum; min = minimum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis; SD = standard deviation

The primary endpoint was the change from Baseline to Week 26 in the MG-ADL total score (a validated patient-reported assessment measuring relevant functional activities affected in patients with gMG).

The secondary endpoints, also assessing changes from Baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score (QMG - a validated clinician-reported assessment of muscle weakness in gMG), the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively, as well as changes in quality-of-life assessments.

ULTOMIRIS demonstrated a statistically significant change in the primary endpoint, change in MG-ADL total score from Baseline to Week 26, as compared to placebo. Primary and secondary endpoint results are presented in Table 26.

The treatment effect of ULTOMIRIS on MG-ADL was rapid, with an improvement demonstrated as early as Week 1 (p = 0.0265) and sustained through Week 26. The efficacy of ULTOMIRIS was consistent overall across pre-specified subgroups (sex, age, body weight, region, immunosuppressant therapy use at Baseline, and MGFA clinical classification).

Table 26 Analysis of Primary and Secondary Efficacy Endpoints in Study ALXN1210-MG-306

Efficacy Endpoints at Week 26	Placebo (N = 89) LS Mean (SEM)	ULTOMIRIS (N = 86) LS Mean (SEM)	Statistic for Comparison	Treatment Effect (95% CI)	p-value (Using Mixed Effect Repeated Measures)
MG-ADL	-1.4 (0.37)	-3.1 (0.38)	Difference in change from baseline	-1.6 (-2.6, -0.7)	0.0009
QMG	-0.8 (0.45)	-2.8 (0.46)	Difference in change from baseline	-2.0 (-3.2, -0.8)	0.0009
QMG ≥5-point improvement	11.3%*	30.0%*	Odds ratio	3.4 (1.4, 7.8)	0.0052
MG-QoL15r	-1.6 (0.70)	-3.3 (0.71)	Difference in change from baseline	-1.7 (-3.4, 0.1)	0.0636
Neuro-QoL-fatigue	-4.8 (1.87)	-7.0 (1.92)	Difference in change from baseline	-2.2 (-6.9, 2.6)	0.3734**
MG-ADL ≥3-point improvement	34.1%*	56.7%*	Odds ratio	2.5 (1.3, 4.8)	0.0049**

*For QMG ≥ 5-point and MG-ADL ≥ 3-point improvement, the adjusted percentages within each treatment are displayed.
** The endpoint was not formally tested for statistical significance; a nominal p-value was reported.
Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QoL15r = Revised Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL-

fatigue = Neurological Quality of Life Fatigue; QMG = Quantitative Myasthenia Gravis; SEM = standard error of mean

The proportion of clinical responders at higher response thresholds (≥ 4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥ 6-, 7-, 8-, 9-, or 10-point improvement on QMG) was consistently greater for ULTOMIRIS compared to placebo.

In patients treated with ULTOMIRIS, improvements were observed in all domain scores of the MG-ADL and in the ocular, bulbar, and limb domain scores of the QMG.

Other Efficacy Results

Overall, 25.6% of patients treated with ULTOMIRIS achieved minimal manifestation status as per the MGFA post-intervention status at Week 26 compared to 9.9% of patients treated with placebo.

Table 27 presents an overview of the patients with clinical deterioration and patients requiring rescue therapy over the 26-week RCP.

Table 27 Clinical Deterioration and Rescue Therapy

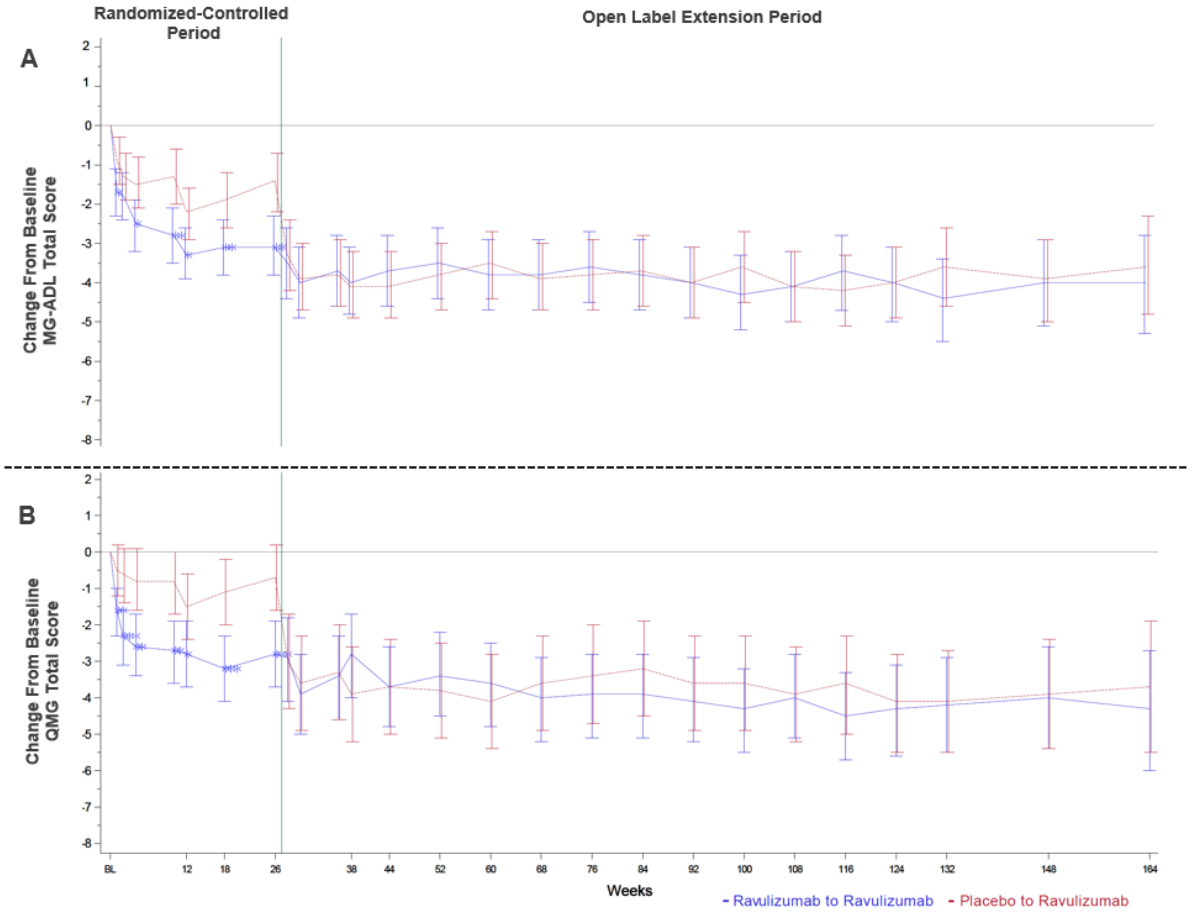
Variable	Statistic	Placebo (N = 89)	ULTOMIRIS (N = 86)
Total number of patients with clinical deterioration	N (%)	15 (16.9)	8 (9.3)
Total number of patients requiring rescue therapy[a]	N (%)	14 (15.7)	8 (9.3)

[a]Rescue therapy included high-dose corticosteroid, plasma exchange/plasmapheresis, or intravenous immunoglobulin.

Long-Term Efficacy

In patients who initially received ULTOMIRIS during the RCP and continued to receive ULTOMIRIS up to 164 weeks in the OLE (median duration of ULTOMIRIS treatment both during RCP and OLE was 108 weeks (759 days), up to a total of 181 weeks (1265 days)), the treatment effect continued to be sustained on all endpoints including MG-ADL and QMG (Figure 5). In patients who initially received placebo during the 26-week RCP and initiated treatment with ULTOMIRIS during the OLE, a rapid and sustained treatment response on all endpoints including MG-ADL and QMG (Figure 5) was observed.

Figure 5 Change from Randomised-Controlled Period Baseline in MG-ADL Total Score (A) and QMG Total Score (B) Up To Week 164 (Mean and 95% CI)



Note: Randomised Controlled Period figures are based on data from 175 patients. Open Label Extension Period figures are based on data from 161 patients.
Abbreviations: CI = confidence interval; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis

Immunosuppressant therapies (IST)

In the OLE of the study, clinicians had the option to adjust IST. At the end of the OLE, 30.1% of patients decreased their daily dose of corticosteroid therapy and 12.4% of patients stopped corticosteroid therapy. The most common reason for change in corticosteroid therapies was improvement in MG symptoms while on ULTOMIRIS treatment.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Study in adult patients with NMOSD

The efficacy of ULTOMIRIS in adult patients with anti-AQP4 antibody-positive NMOSD was assessed in a global, open-label clinical study (ALXN1210-NMO-307).

Study ALXN1210-NMO-307 enrolled 58 adult patients with NMOSD who had a positive serologic test for anti-AQP4 antibodies, at least 1 relapse in the last 12 months prior to the Screening Period, and an Expanded Disability Status Scale (EDSS) score of ≤ 7. Prior treatment with immunosuppressant therapies (ISTs) was not required for enrolment and 51.7% of patients were on ULTOMIRIS monotherapy. Patients on selected ISTs (ie, corticosteroids, azathioprine, mycophenolate mofetil, tacrolimus) were permitted to continue on therapy in combination with ULTOMIRIS, with a requirement for stable dosing until they reached Week 106 in the study. In addition, acute therapy for relapse treatment (including high-dose corticosteroids, PE/PP, and IVIg) was allowed if a patient experienced a relapse during the study.

Patients included in the study had a mean age of 47.4 years (ranging from 18 to 74 years) and most of them were female (90%). Median age at NMOSD initial clinical presentation was of 42.5 years, ranging from 16 to 73 years. Baseline disease characteristics are shown in Table 28.

Table 28 Patient disease history and baseline characteristics in study ALXN1210-NMO-307

Variable	Statistic	ULTOMIRIS (n = 58)
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Mean (SD) Median Min, max	5.2 (6.38) 2.0 0.19, 24.49
Historical ARR within 24 months prior to screening	Mean (SD) Median Min, max	1.87 (1.59) 1.44 0.5, 6.9
Baseline HAI score	Mean (SD) Median Min, max	1.2 (1.42) 1.0 0, 7
Baseline EDSS score	Mean (SD) Median Min, max	3.30 (1.58) 3.25 0.0, 7.0
Any historical rituximab use	n (%)	21 (36.2)
Number of patients receiving stable corticosteroids only at study entry	n (%)	12 (20.7)
Number of patients not receiving any IST at study entry	n (%)	30 (51.7)

Abbreviations: ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; IST = immunosuppressant therapy; Max = maximum; Min = minimum; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation.

The primary endpoint of Study ALXN1210-NMO-307 was the time to first adjudicated on-trial relapse as determined by an independent adjudication committee. No adjudicated on-trial relapse was observed in ULTOMIRIS-treated patients during the Primary Treatment Period.

A pre-specified indirect comparison of the ULTOMIRIS arm of the study with an external placebo arm (placebo arm of the Phase 3 Study ECU-NMO-301) showed a relative relapse risk reduction of 98.6% compared to placebo (hazard ratio: 0.014; $p < 0.0001$).

All ULTOMIRIS-treated patients remained relapse free over the median follow-up of 90.93 weeks. ULTOMIRIS-treated patients experienced consistent relapse-free primary endpoint result with or without concomitant IST treatment.

ULTOMIRIS-treated patients had an adjudicated on-trial annualised relapse rate (ARR) that was statistically significantly lower than the predicted ARR of 0.25 (1 adjudicated on-trial relapse per 4 patient -years) ($p < 0.0001$). The 0.25 comparator rate was chosen to represent a conservative ARR that may be experienced in the NMOSD patient population.

Of the 58 ULTOMIRIS-treated patients, 96.6% and 89.7% did not experience clinically important worsening in Hauser Ambulation Index score and Expanded Disability Status Scale during the Primary Treatment Period, respectively.

ULTOMIRIS has not been studied for the acute treatment of relapses in NMOSD patients.

5.2 PHARMACOKINETIC PROPERTIES

A linear, 2-compartment PK model was developed that adequately described the observed ravulizumab *rch* PK following IV administration. The estimated mean (SD) clearance, central volume, volume at steady state and terminal elimination half-life following multiple dosing of ravulizumab *rch* in adult and paediatric patients with PNH or aHUS and in adult patients with gMG and NMOSD are provided in Table 29.

In patients with PNH, aHUS, gMG or NMOSD pharmacodynamic activity correlates directly with ravulizumab *rch* serum concentrations above the target exposure level results in free C5 levels < 0.5 µg/mL, achieving immediate, complete and sustained blockade of terminal complement inhibition in all patients.

Absorption

Because ravulizumab *rch* administration is via an IV infusion and the dosage form is a solution, 100% of the administered dose is considered bioavailable. The time to maximum observed concentration (t_{max}) is expected to be at the end of infusion (EOI) or soon after EOI. Over the studied dose and regimen range, ravulizumab *rch* exhibited dose proportional and time linear pharmacokinetics (PK).

Distribution

The mean (standard deviation [SD]), central volume and volume of distribution at steady state in adult and paediatric patients with PNH, aHUS or adult patients with gMG and NMOSD treated with ravulizumab *rch* are presented in Table 29.

Metabolism and Excretion

As an IgG monoclonal antibody, ravulizumab *rch* is expected to be metabolised in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab *rch* contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab *rch* in patients with PNH, aHUS, gMG or NMOSD treated with ravulizumab *rch* are presented in Table 29.

Body weight was a significant covariate on the pharmacokinetics of ravulizumab *rch*.

Table 29 Estimated Central Volume, Distribution, Biotransformation and Elimination Parameters Following Ravulizumab *rch* Treatment

	Adult and Paediatric Patients with PNH	Adult and Paediatric Patients with aHUS	Adult Patients with gMG	Adult Patients with NMOSD
Estimated central volume (litres) Mean (SD)	Adults: 3.44 (0.66) Paediatrics: 2.87 (0.60)	Adults: 3.25 (0.61) Paediatrics: 1.14 (0.51)	3.42 (0.756)	2.91 (0.571)
Volume of distribution at steady state (litres) Mean (SD)	5.30 (0.9)	5.22 (1.85)	5.74 (1.16)	4.77 (0.819)
Terminal elimination half-life (days) Mean (SD)	49.6 (9.1)	51.8 (16.2)	56.6 (8.36)	64.3 (11.0)
Clearance (litres/day) Mean (SD)	0.08 (0.022)	0.08 (0.04)	0.08 (0.02)	0.05 (0.016)

PK parameters for ravulizumab *rch* are consistent across PNH, aHUS, gMG and NMOSD patient populations.

Special Populations

No formal trial of the effect of sex, race, age (elderly), hepatic or renal impairment on the pharmacokinetics of ravulizumab *rch* was conducted. However, based on population-PK assessment, no impact of sex, age, race and hepatic or renal function on ravulizumab *rch* PK was identified in the studied healthy volunteer subjects and patients with PNH, aHUS, gMG or NMOSD and as a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab *rch* have been studied in aHUS patients with a range of renal impairment, including patients receiving dialysis. There have been no observed differences in pharmacokinetic parameters noted in these sub-populations, including patients with proteinuria.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of ravulizumab *rch.*

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of ravulizumab *rch.*

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

monobasic sodium phosphate
dibasic sodium phosphate
polysorbate 80
L-arginine
sucrose
water for injections

ULTOMIRIS 100 mg/mL contains 4.6 mg sodium per 3 mL vial or 16.8 mg sodium per 11 mL vial. This should be taken into consideration by patients on a controlled sodium diet.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Reconstitution and dilution should only use 0.9% sodium chloride, solution for injection as diluent.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ULTOMIRIS vials must be stored under refrigerated conditions at 2°C – 8°C.

After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product have been demonstrated for up to 24 hours at 2°C-8°C and up to 4 hours at room temperature.

Vials must not be frozen or shaken.

Keep the vial in the outer carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass vial with a stopper and a seal.

Pack size of one vial.

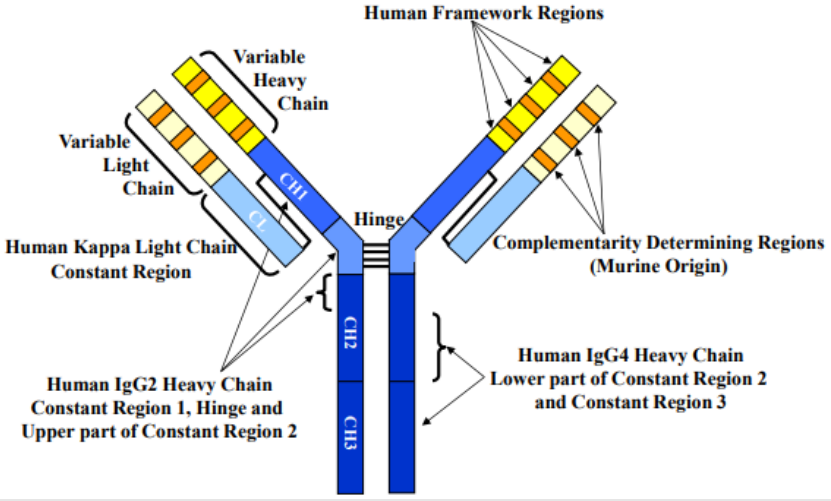
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

CAS registry number: 1803171-55-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
Level 4, 66 Talavera Road
Macquarie Park NSW 2113

Medical enquiries: 1800 788 189

9 DATE OF FIRST APPROVAL

23 March 2021

10 DATE OF REVISION

14 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2, 4.3, 4.8, 5.1	Minor editorial changes.
4.8	Correction of an error.