ULTOMIRIS®
(ravulizumab)

1. NAME OF THE MEDICINAL PRODUCT

ULTOMIRIS 300 mg/3 mL concentrate for solution for infusion
ULTOMIRIS 1100 mg/11 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ULTOMIRIS is a formulation of ravulizumab which is a long-acting humanized monoclonal IgG2/4K antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

For the full list of excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

ULTOMIRIS 100 mg/mL.

Translucent, clear to yellowish color, pH 7.4 solution.

Each vial of 3 mL contains 300 mg of ravulizumab (100 mg/mL).
Each vial of 11 mL contains 1100 mg of ravulizumab (100 mg/mL).

After dilution, the final concentration of the ULTOMIRIS 100 mg/mL solution to be infused is 50 mg/mL.

Excipient(s) with known effect: Sodium (4.6 mg per 3 mL vial or 16.8 mg per 11 mL vial).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paroxysmal Nocturnal Hemoglobinuria

ULTOMIRIS is indicated for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH)

- who presents with clinical symptom(s) indicative of high disease activity.
- who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Atypical Hemolytic Uremic Syndrome

ULTOMIRIS is indicated for the treatment of adult and pediatric patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitations of Use:
ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Generalized Myasthenia Gravis

ULTOMIRIS is indicated as an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

4.2 Posology and method of administration

Posology

Intravenous (IV) Use

Adult and pediatric patients with PNH or aHUS with body weight greater than or equal to 5 kg.

The recommended ULTOMIRIS maintenance dosing in adult and pediatric patients with PNH or aHUS with a body weight greater than or equal to 5 kg is based on the patient's body weight, as shown in Table 1, with maintenance doses administered every 4 or 8 weeks, starting 2 weeks after loading dose.

Refer to Table 2 for treatment initiation instructions in patients who are complement inhibitor treatment-naïve or switching treatment from SOLIRIS.

Dosing schedule is allowed to occasionally vary 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.

Adult patients with gMG with body weight greater than or equal 40 kg.

The recommended ULTOMIRIS maintenance dosing in adult patients with gMG with a body weight greater than or equal to 40 kg is based on the patient's body weight, as shown in Table 1, with maintenance doses administered every 8 weeks, starting 2 weeks after loading dose.

Refer to Table 2 for treatment initiation instructions in patients who are complement inhibitor treatment-naïve or switching treatment from SOLIRIS.

Dosing schedule is allowed to occasionally vary 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.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

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
≥ 40 to < 60	2400	3000	Every 8 weeks
≥ 60 to < 100	2700	3300	Every 8 weeks

Body Weight Range (kg)	Loading dose (mg)*	Maintenance dose (mg)	Dosing interval
≥ 100	3000	3600	Every 8 weeks

*See Table 4 for ULTOMIRIS loading dose instructions prior to maintenance dosing.
**For PNH and aHUS indications only.

Table 2: ULTOMIRIS Treatment Initiation Instructions

Population	Weight-based ULTOMIRIS Loading Dose	Time of First ULTOMIRIS Weight-based Maintenance Dose
Not currently on ULTOMIRIS or SOLIRIS treatment	At treatment start	2 weeks after ULTOMIRIS loading dose
Currently treated with SOLIRIS	At time of next scheduled SOLIRIS dose	2 weeks after ULTOMIRIS loading dose

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
	3300	1800	
≥ 100	3000	1500	600
	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

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

Method of Administration

Intravenous (IV) Use

ULTOMIRIS is for administration by a healthcare provider and is not intended for subcutaneous administration.

This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.

For instructions on dilution of the medicinal product before administration, see Section 8.1.

ULTOMIRIS 100 mg/mL

ULTOMIRIS 100 mg/mL must be diluted to a final concentration of 50 mg/mL.

Following dilution, ULTOMIRIS 100 mg/mL is to be administered by intravenous infusion based on body weight as shown in Table 4 and Table 5.

Table 4: Loading and Maintenance Dose Administration Rate for ULTOMIRIS 100 mg/mL

Body Weight Range (kg)[a]	**Loading dose (mg)**	**Minimum infusion duration minutes (hours)**	**Maintenance dose (mg)**	**Minimum infusion duration minutes (hours)**
≥ 5 to < 10*	600	85 (1.4)	300	45 (0.8)
≥ 10 to < 20*	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30*	900	35 (0.6)	2100	75 (1.3)
≥ 30 to < 40*	1200	31 (0.5)	2700	65 (1.1)
≥ 40 to < 60	2400	45 (0.8)	3000	55 (0.9)
≥ 60 to < 100	2700	35 (0.6)	3300	40 (0.7)
≥ 100	3000	25 (0.4)	3600	30 (0.5)

* For PNH and aHUS indications only.
[a] Body weight at time of treatment.

Table 5: Supplemental Dose Administration Rate for ULTOMIRIS 100 mg/mL

Body Weight Range (kg)[a]	**Supplemental dose (mg)**	**Minimum infusion duration minutes (hr)**
≥ 40 to < 60	600	15 (0.25)
	1200	25 (0.42)
	1500	30 (0.5)
≥ 60 to < 100	600	12 (0.20)
	1500	22 (0.36)
	1800	25 (0.42)
≥ 100	600	10 (0.17)
	1500	15 (0.25)
	1800	17 (0.28)

[a] Body weight at time of treatment.

Special Populations

Women of Childbearing Potential

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

Pediatric Population/Use in children

Use of ULTOMIRIS in pediatric patients for treatment of PNH is supported by evidence from a pediatric clinical study (13 patients aged 9 to 17 years). The safety and efficacy of ULTOMIRIS for the treatment of pediatric and adult patients with PNH appear similar. See Section 6.1.

Use of ULTOMIRIS in pediatric patients for treatment of aHUS is supported by evidence from a pediatric clinical study (14 patients aged 10 months to 17 years). The safety and efficacy of ULTOMIRIS for the treatment of aHUS is consistent in pediatric and adult patients.

ULTOMIRIS has not been studied in PNH patients below 9 years of age. The posology to be used in pediatric patients with PNH is identical to the weight-based dosing recommendations provided for pediatric patients with aHUS, with maintenance dosing starting 2 weeks after loading dose administration. Based on the PK/PD data available in aHUS and PNH patients treated with ULTOMIRIS, this dosing regimen is expected to result in an efficacy and safety profile similar to that in adults, for all pediatric patients starting at 5 kg.

ULTOMIRIS has not been evaluated in pediatric patients with gMG.

Use in the Elderly

ULTOMIRIS may be administered to patients aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population.

Patients with Aplastic Anemia

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

Renal and Hepatic Impairment

Studies have not been conducted to examine the effects of hepatic impairment; however, pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment.

No dose adjustment is required for patients with renal impairment, see Section 5.2.

The clinical trials of ULTOMIRIS in patients with aHUS included patients with other complement-mediated TMA conditions (patients with renal impairment, some of whom were receiving dialysis). No dose adjustment is required in this population, see Section 5.2.

4.3 Contraindications

- Do not initiate ULTOMIRIS therapy in patients with unresolved *Neisseria meningitidis* infection.

- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see Section 4.4).

4.4 Special warnings and special 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 disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to, or at the time of, initiating ULTOMIRIS. 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 in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. In clinical studies with ULTOMIRIS, 4 patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS. Consideration should be given to official guidance on the appropriate use of antibacterial agents. 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/Parent Guide and a Patient card/Patient safety card.

Immunization

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS) or MG exacerbation (gMG). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

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 information from the Patient/Parent Guide to increase their awareness of potential serious infections and their signs and symptoms. Physicians should advise patients about gonorrhoea prevention. 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.

Infusion Reactions

Intravenous (IV) administration of ULTOMIRIS may result in systemic infusion reactions (infusion-related reactions) that cause allergic or hypersensitivity reactions (including anaphylaxis).

In case of a systemic infusion reaction (infusion-related reaction), if signs of cardiovascular instability or respiratory compromise occur, administration of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted.

Immunogenicity

Treatment with any therapeutic protein may induce an immune response.

In ULTOMIRIS studies in PNH (N = 488), aHUS (N = 89), and gMG (N = 86), treatment-emergent anti-drug antibodies were reported in 2 patients (0.28%), one with PNH and one with aHUS. These anti-drug antibodies were transient in nature with low titer and did not correlate with clinical response or adverse events.

4.5 Treatment discontinuation

Treatment Discontinuation in PNH

Paroxysmal Nocturnal Hemoglobinuria (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 hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), 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 hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Treatment Discontinuation in aHUS

ULTOMIRIS treatment to resolve aHUS should be a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy.

There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (SOLIRIS) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.
If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe 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 ravulizumab treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ravulizumab treatment; or, an increase in serum

LDH of 25% or more as compared to baseline or to nadir during ravulizumab treatment; (results should be confirmed by a second measurement 28 days apart).
Or

(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 ravulizumab discontinuation, consider reinitiation of ravulizumab treatment beginning with the loading dose and maintenance dose described in Section 4.2.

Treatment Discontinuation in gMG

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

4.6 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been performed.

See Section 4.2 for guidance in case of concomitant PE, PP, or IVIg treatment.

4.7 Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available.

Nonclinical reproductive toxicology studies were not conducted with ravulizumab. Reproductive toxicology studies were conducted in mice using the murine surrogate molecule BB5.1, which assessed effect of C5 blockade on the reproductive system. No specific test-article related reproductive toxicities were identified in these studies. Human IgG are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in fetal circulation.

Lactation

It is unknown whether ravulizumab 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 up to 8 months after treatment.

Nonclinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to pups resulting from consuming milk from treated dams.

Fertility

No specific non-clinical study on fertility has been conducted with ravulizumab.

Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on fertility of the treated females or males.

4.8 Effect on ability to drive and use machines

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

4.9 Undesirable effects

Summary of the Safety Profile

The most common adverse drug reactions (≥ 10%) across all clinical trials are headache, upper respiratory tract infection, nasopharyngitis, and diarrhoea. The most serious adverse reactions in patients in clinical trials are meningococcal infections.

Tabulated List of Adverse Reactions

Table 6 lists the adverse reactions observed from clinical trials and post-marketing experience. Adverse reactions with ULTOMIRIS are listed by System Organ Class and preferred term using MedDRA frequency 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 the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse Reactions from Clinical Trials & Post-marketing Experience[a]

MedDRA System Organ Class	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)
Gastrointestinal disorders	Diarrhoea, Nausea	Vomiting, Abdominal pain, Dyspepsia			
General disorders and administration site conditions	Fatigue	Pyrexia, Influenza like illness, Asthenia	Chills		
Immune system disorders			Anaphylactic reaction[a], Hypersensitivity[b]		
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis		Meningococcal infection, Meningococcal sepsis, Gonococcal infection[c]		
Injury, poisoning and procedural complications		Infusion-related reaction			

MedDRA System Organ Class	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)
Musculoskeletal and connective tissue disorders		Arthralgia, Back pain, Myalgia, Muscle spasms			
Nervous system disorders	Headache	Dizziness			
Skin and subcutaneous tissue disorders		Urticaria, Pruritus, Rash			

[a] Estimated postmarketing experience based on 2020-Dec-31 cutoff from PSUR (Periodic Safety Update report).
[b] Hypersensitivity is a group term for Preferred Term drug hypersensitivity with related causality and Preferred Term hypersensitivity.
[c] Gonococcal infection includes disseminated gonococcal infection; data based on 2021-Dec-31 cutoff date from Development Safety Update Report (DSUR).
Source: Data on file based on 52-week data cutoff from Phase 3 PNH Studies ALXN1210 PNH 301 (2018 Sep 04) and ALXN1210 PNH 302 (2018-Sep-07); 52 week data cutoff from Phase 3 complement mediated TMA Studies ALXN1210-aHUS-311 (2019-Oct-10) and ALXN1210 aHUS 312 (2020 Jan-28); 90 day safety update for Study ALXN1210 PNH 103 (2018-Apr-23), Study ALXN1210 PNH-201 (2018-May-15), and Study ALXN1210 PNH 304 (2020-Dec-01); and 60-week data cutoff from gMG Study ALXN1210 MG 306 (2021-Nov-09).

Description of Selected Adverse Reactions

In clinical studies, the most serious adverse reactions from ULTOMIRIS were meningococcal infections, which were uncommon in frequency (0.5%) (see Section 4.4). Meningococcal infections in patients treated with ULTOMIRIS have presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicemia and advised to seek medical care immediately.

Infusion Reactions

In clinical trials, infusion reactions (infusion-related reactions) were common (1.6%). They were mild to moderate in severity and transient (e.g., lower 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). These reactions did not require discontinuation of ULTOMIRIS.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorization 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 via their national reporting system.

Pediatric Population

In children and adolescent PNH patients (aged 9 to 17 years old) included in the pediatric PNH Study (ALXN1210-PNH-304), the safety profile of ULTOMIRIS was consistent with that observed in adult PNH patients. The most common adverse reaction reported in pediatric PNH patient was abdominal pain and nasopharyngitis.

In pediatric aHUS patients (aged 10 months to 17 years old) included in Study ALXN1210-aHUS-312, the safety profile of ULTOMIRIS was consistent with that observed in adult patients with evidence of aHUS. The safety profile was also consistent for pediatric patients in the different age-group subsets. The safety data for patients below 2 years of age are limited to four patients. The most common adverse reaction reported in pediatric patients was pyrexia.

ULTOMIRIS has not been evaluated in pediatric patients with gMG

Geriatric Population

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years) with ULTOMIRIS.

4.10 Overdose

No case of overdose has been reported to date.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA43

Ravulizumab is a humanized 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 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.

5.1 Pharmacodynamic properties

Mechanism of Action

Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, and cell lysis while preserving the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

This mechanism of action provides the therapeutic rationale for the use of ULTOMIRIS in PNH, complement-mediated TMA, gMG in which uncontrolled complement activation is involved. In patients with PNH, complement-mediated intravascular hemolysis is blocked with ULTOMIRIS treatment. ULTOMIRIS resolves complement-mediated TMA. In gMG patients, ULTOMIRIS inhibits terminal complement activation, which otherwise leads to MAC deposition at the neuromuscular junction resulting in impairment of neuromuscular transmission.

Ravulizumab was specifically engineered to dissociate from C5 and associate with human neonatal Fc receptor (FcRn) at pH 6.0 (with minimal 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 terminal elimination half-life (see Section 5.2).

ULTOMIRIS dosing has been optimized 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, that is sustained throughout the dosing interval.

This dosing regimen provides prolonged pharmacologic activity, based on the half-life of ravulizumab in serum, and allows dosing once every 8 weeks (or once every 4 weeks for patients weighing less than 20 kg).

Pharmacodynamic Effects

Following ULTOMIRIS treatment in both adult and pediatric complement-inhibitor naïve patients and SOLIRIS-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 in all patients. In contrast, serum free C5 concentrations did not consistently remain < 0.5 μg/mL following SOLIRIS treatment.

Following ULTOMIRIS treatment, immediate and complete inhibition of serum free C5 was also observed in adult and pediatric patients with complement-mediated TMA and adult patients with gMG 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, complement-mediated TMA, gMG, following ULTOMIRIS treatment. Free C5 levels of < 0.5 μg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition.

Clinical Efficacy and Safety

Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of ULTOMIRIS in adult patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:

- a complement-inhibitor naïve study in adult patients with PNH who were naïve to complement inhibitor treatment,
- a SOLIRIS-experienced study in adult patients with PNH who were clinically stable after having been treated with SOLIRIS (eculizumab) for at least the previous 6 months.

ULTOMIRIS was dosed in accordance with the recommended dosing described in Section 4.2 (4 infusions of ULTOMIRIS over 26 weeks) while SOLIRIS was administered according to the approved dosing regimen of SOLIRIS of 600 mg every week for the first 4 weeks and 900 mg every 2 weeks (15 infusions over 26 weeks).

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. The 12-month transfusion history was similar between ULTOMIRIS and SOLIRIS treatment groups within each of the Phase 3 studies.

Study in Complement-Inhibitor Naïve Adult Patients with PNH

The Complement-Inhibitor Naïve Study was a 26-week, multicenter, open-label, randomized, active-controlled, Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry. Eligible patients to enter this trial had to demonstrate high disease activity, defined as LDH level ≥ 1.5 × upper limit of normal (ULN) at screening along with the presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.

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 × ULN, which is a direct measurement of intravascular haemolysis, in the setting of PNH.

Table 7 presents the baseline characteristics of the PNH patients enrolled in the Complement-Inhibitor Naïve Study, with no apparent clinically meaningful differences observed between the treatment arms.

Table 7: 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 cell (pRBC) transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)

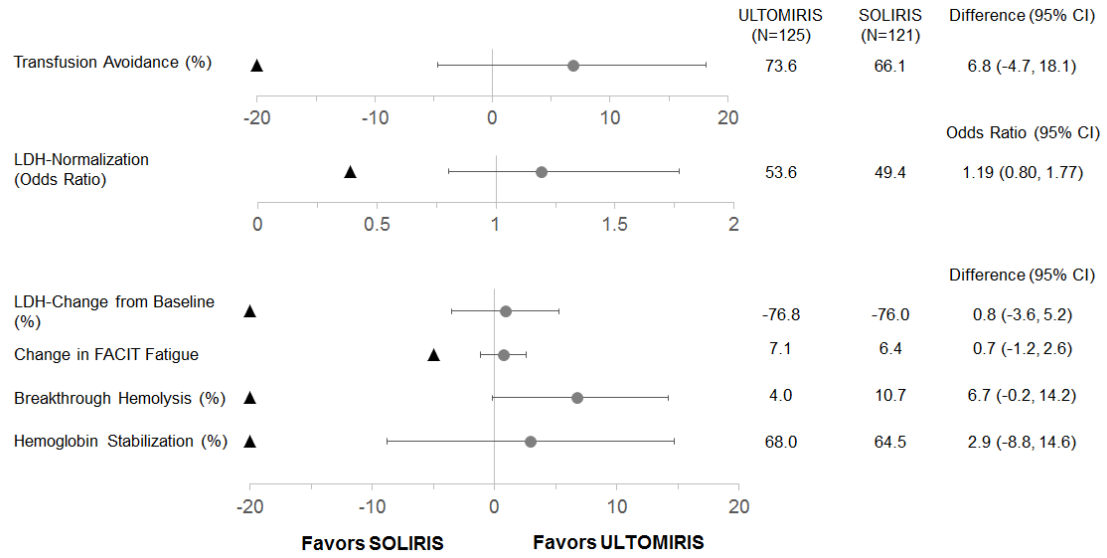
Parameter	Statistics	ULTOMIRIS (N = 125)	SOLIRIS (N = 121)
Units of pRBC transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Total PNH RBC clone size	Median	33.6	34.2
Total PNH granulocyte clone size	Median	93.8	92.4
Patients with any PNH conditions[a] prior to informed consent	n (%)	121 (96.8)	120 (99.2)
Anemia		103 (82.4)	105 (86.8)
Hematuria or hemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anemia		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[b]		27 (21.6)	13 (10.7)

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

The coprimary endpoints were transfusion avoidance, and hemolysis as directly measured by normalization of LDH levels (LDH levels ≤ 1 × ULN; the ULN for LDH is 246 U/L). 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 hemolysis, and proportion of patients with stabilized hemoglobin.

ULTOMIRIS was non-inferior compared to eculizumab for both coprimary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines and LDH normalisation from day 29 to day 183, and for all 4 key secondary endpoints (Figure 1).

Figure 1: Analysis of Coprimary 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.
Note: LDH = lactate dehydrogenase, CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

Study in Adult PNH Patients Previously Treated with SOLIRIS

The SOLIRIS-Experienced Study was a 26-week, multicenter, open-label, randomized, active-controlled Phase 3 study conducted in 195 patients with PNH who were clinically stable (LDH ≤ 1.5 x ULN) after having been treated with SOLIRIS for at least the past 6 months.

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. The mean total PNH RBC clone size was 60.05%, mean total PNH granulocyte clone size was 83.30%, and the mean total PNH monocyte clone size was 85.86%.

Table 8 presents the baseline characteristics of the PNH patients enrolled in the SOLIRIS-Experienced Study, with no apparent clinically meaningful differences observed between the treatment arms.

Table 8: 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)

Parameter	Statistics	ULTOMIRIS (N = 97)	SOLIRIS (N = 98)
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)
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[a] prior to informed consent	n (%)	90 (92.8)	96 (98.0)
Anemia		64 (66.0)	67 (68.4)
Hematuria or hemoglobinuria		47 (48.5)	48 (49.0)
Aplastic anemia		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[b]		14 (14.4)	14 (14.3)

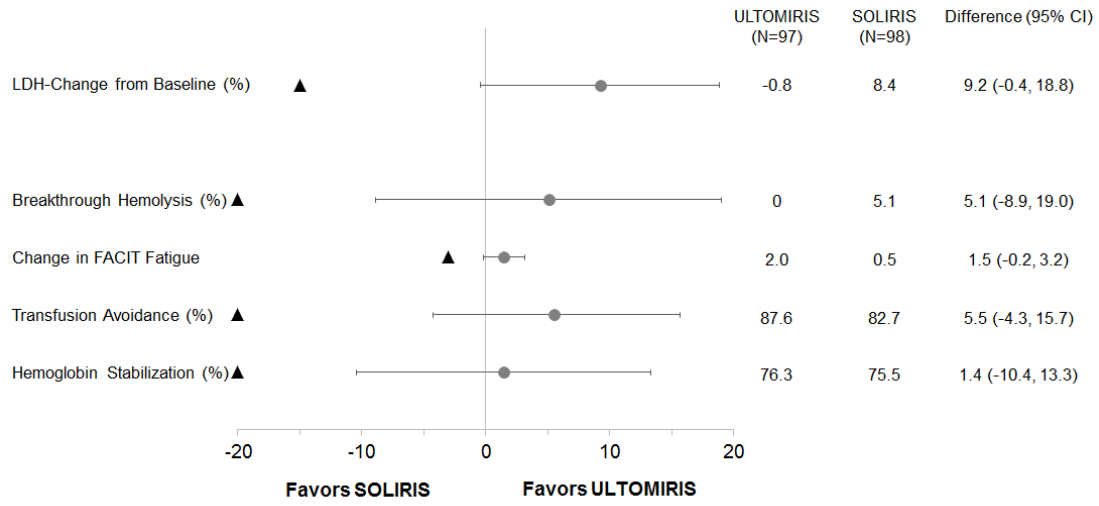
[a] Based on medical history.

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

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

ULTOMIRIS was non-inferior compared to eculizumab for the primary endpoint, percent change in LDH from baseline to day 183, and for all 4 key secondary endpoints (Figure 2).

Figure 2: Analysis of Primary and Secondary Endpoints – Full Analysis Set (SOLIRIS-Experienced Study)



Note: The black triangle indicates the noninferiority margins, and grey dot indicates point estimates.
Note: LDH = lactate dehydrogenase, CI = confidence interval

Atypical Hemolytic Uremic Syndrome (aHUS)

Study in Adult Patients with aHUS

The adult study was a multicenter, single arm, Phase 3 study conducted in patients with documented aHUS who were naïve to complement inhibitor treatment prior to study entry and had evidence of thrombotic microangiopathy (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 patient presenting with TMA due to a thrombotic thrombocytopenic purpura (TTP), Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS). Two patients were excluded from the Full Analysis Set due to a confirmed diagnosis of STEC-HUS. Ninety-three percent of patients had extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline.

Table 9 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 9: Baseline Characteristics in the Adult Study

Parameter	**Statistics**	**Ravulizumab (N = 56)**
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male	 n (%)	 19 (33.9)
Race [a] Asian White Other	n (%)	 15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelets (10^9/L) blood	n Median (min, max)	56 95.25 (18, 473)
Hemoglobin (g/L) blood	n Median (min, max)	56 85.00 (60.5, 140)
LDH (U/L) serum	n Median (min, max)	56 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2)	n (%) Median (min, max)	55 10.00 (4, 80)
Patients on dialysis	N (%)	29 **(**51.8)
Patients post partum	N (%)	8 (14.3)

Note: Percentages are based on the total number of patients.
Abbreviations: aHUS = atypical hemolytic uremic 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 normalization of hematological parameters (platelet count ≥ 150 x 10^9/L and LDH ≤ 246 U/L) 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.

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week Initial Evaluation Period as shown in Table 10.

Table 10: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (ALXN1210-aHUS-311)

	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 normalization	56	47	0.839 (0.734, 0.944)
LDH normalization	56	43	0.768 (0.648, 0.887)
≥25% improvement in serum creatinine from baseline	56	33	0.589 (0.452, 0.727)
Hematologic normalization	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.

Four additional patients had a Complete TMA Response that was confirmed after the 26-week Initial_Evaluation Period (with a Complete TMA Response occurring at Days 169, 302, 401 and 407) resulting in an overall Complete TMA Response in 34 of 56 patients (60.7%; 95% CI: 47.0%, 74.4%). Individual component response increased to 48 (85.7%; 95% CI: 75.7%, 95.8%) patients for platelet count normalization, 47 (83.9%; 95% CI: 73.4%, 94.4%) patients for LDH normalization, and 35 (62.5%; 95% CI: 48.9%, 76.1%) patients for renal function improvement.

Complete TMA Response was achieved at a median time of 86 days (7 to 169 days). An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 118.52 × 10^9/L at baseline to 240.34 ×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, 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).

Of the patients who presented at CKD Stage 5, 67.6% (23/34) showed an improvement of 1 or more 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. 17 of the 29 patients who required dialysis at study entry were able to discontinue dialysis by the end of the available follow-up while 6 of 27 patients who were off dialysis at baseline were on dialysis at last available follow-up. Table 11 summarizes the secondary efficacy outcomes for Study ALXN1210-aHUS-311.

Table 11: Secondary Efficacy Outcome for Study ALXN1210-aHUS-311

Parameters	**Study ALXN1210-aHUS-311 (N = 56)**	
Hematologic 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 hemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/n	40/56	
Proportion (95% CI)*	0.714 (0.587, 0.842)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	32/47	
Proportion (95% CI)*	0.681 (0.529, 0.809)	
Worsened[b]		
m/n	2/13	
Proportion (95% CI)*	0.154 (0.019, 0.454)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=48)	Change from baseline (n=47)
Mean (SD)	51.83 (39.162)	34.80 (35.454)
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.
*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper-Pearson method. [a]Excludes those with CKD Stage 1 at baseline as they cannot improve. [b]Excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Generalized Myasthenia Gravis (gMG)

Study in Adult Patients with gMG

The efficacy and safety of ULTOMIRIS in adult patients with gMG was assessed in a Phase 3, randomized, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306). Patients participating in this study 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 remaining symptomatology as evidenced by a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 6 were randomized to receive either ULTOMIRIS (N = 86) or placebo (N = 89). Patients on immunosuppressant therapies (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 are presented in Table 12. The majority (97%) of patients included in the study had been treated with at least one immunomodulatory therapy including immunosuppressant therapies, PE/PP, or IVIg in the last two years prior to enrolment.

Table 12: Baseline Disease Characteristics in Study ALXN1210-MG-306

Parameter	**Statistics**	**Placebo (N = 89)**	**ULTOMIRIS (N = 86)**
Sex Male Female	n (%)	 44 (49.4) 45 (50.6)	 42 (48.8) 44 (51.2)
Age at first dose of study drug (years)	Mean (SD) (min, max)	53.3 (16.05) (20, 82)	58.0 (13.82) (19, 79)
Elderly (≥ 65 years of age) at study entry	n (%)	24 (27.0)	30 (34.9)
Duration of MG since diagnosis (years)	Mean (SD) (min, max) Median	10.0 (8.90) (0.5, 36.1) 7.6	9.8 (9.68) (0.5, 39.5) 5.7
Baseline MG-ADL Score	Mean (SD) (min, max) Median	8.9 (2.30) (6.0, 15.0) 9.0	9.1 (2.62) (6.0, 24.0) 9.0
Baseline QMG Score	Mean (SD) (min, max) Median	14.5 (5.26) (2.0, 27.0) 14.0	14.8 (5.21) (6.0, 39.0) 15.0
Baseline MGFA classification Class II (mild weakness) Class III (moderate weakness) Class IV (severe weakness)	n (%)	 39 (44) 45 (51) 5 (6)	 39 (45) 41 (48) 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)

Parameter	Statistics	Placebo (N = 89)	ULTOMIRIS (N = 86)
Number of stable immunosuppressant therapies[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)

[a] Prior MG crisis information were collected as part of medical history and not evaluated as per the clinical protocol definition.

[b] Immunosuppressant therapies include corticosteroids, 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.

The secondary endpoints, also assessed changes from baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score, 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 MG-ADL total score as compared to placebo. Primary and secondary endpoint results are presented in Table 13.

Table 13: Analysis of Primary and Secondary Efficacy Endpoints

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
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[a]

[a] 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.

In Study ALXN1210-MG-306, a clinical responder in the MG-ADL total score was defined as having at least a 3-point improvement. The proportion of clinical responders at Week 26 was 56.7% on ravulizumab compared with 34.1% on placebo (nominal p=0.0049). A clinical responder in the QMG total score was defined as having at least a 5-point improvement. The proportion of clinical responders at Week 26 was 30.0% on ravulizumab compared with 11.3% on placebo (p=0.0052).

Table 14 presents an overview of the patients with clinical deterioration and patients requiring rescue therapy over the 26-week RCP.

Table 14: Clinical Deterioration and Rescue Therapy

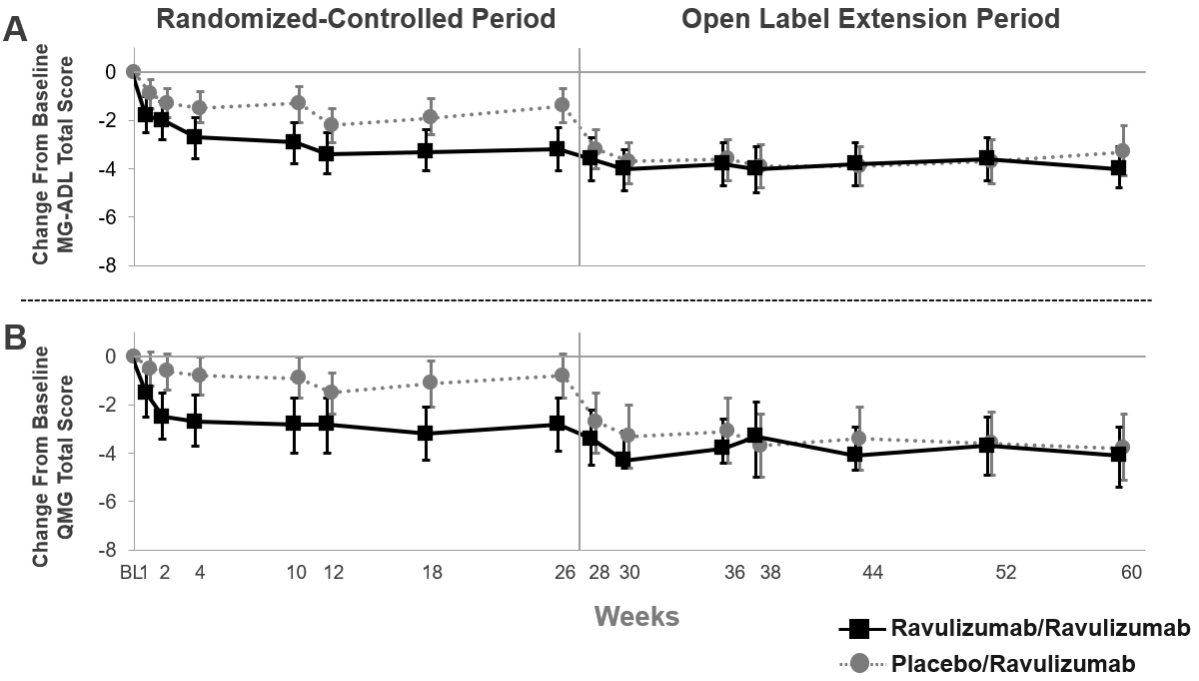
Variable	**Statistic**	**Placebo (N = 89)**	**ULTOMIRIS (N = 86)**
Total number of patients with clinical deterioration	n (%)	15 (16.9)	8 (9.3)
Total number of patients requiring rescue therapy[a]	n (%)	14 (15.7)	8 (9.3)

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

At the time of the analysis, 150 of the 158 patients who entered the Open-Label Extension Period were ongoing in the study.

In patients who initially received ULTOMIRIS during the RCP and continued to receive ULTOMIRIS during the first 26 weeks of the OLE, the treatment effect was sustained (Figure 3). 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 (Figure 3), was observed.

Figure 3: Change from Randomized-Controlled Period Baseline in MG-ADL Total Score (A) and QMG Total Score (B) Through Week 60 (Mean and 95% CI)



Abbreviations: CI = confidence interval; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis

In the OLE of the study, clinicians had the option to adjust immunosuppressant therapies. In patients followed for 34 weeks in the OLE, 28.0% of patients decreased their daily dose of corticosteroid therapy and 6.2% of patients stopped corticosteroid therapy. The most common reason for change in corticosteroid therapies was improvement in MG symptoms while on ULTOMIRIS treatment.

Pediatric Population

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Study in Pediatric Patients with PNH

The pediatric study (ALXN1210-PNH-304) is a multi-center, open-label, Phase 3 study conducted in SOLIRIS-experienced and complement inhibitor-naïve pediatric patients with PNH.

From interim results, a total of 13 PNH pediatric 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 inhibitor and 8 patients received treatment with SOLIRIS prior to study entry.

Most of the patients were between 12 and 17 years of age at first infusion (mean: 14.4 years), with 2 patients under 12 years old (11 and 9 years old). Eight of the 13 patients were female. Mean weight at baseline was 56 kg, ranging from 37 to 72 kg. Table 15 presents the baseline disease history and characteristics of the paediatric patients enrolled in Study ALXN1210 PNH-304.

Table 15: Disease History and Characteristics at Baseline (Full Analysis Set)

Variable	Complement inhibitor-naïve patients (N = 5)	Eculizumab-experienced patients (N = 8)
Total PNH RBC clone size (%)	(N = 4)	(N = 6)
Median (min, max)	40.05 (6.9, 68.1)	71.15 (21.2, 85.4)
Total PNH granulocyte clone size (%)		
Median (Min, max)	78.30 (36.8, 99.0)	91.60 (20.3, 97.6)
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)
Anemia	2 (40.0)	5 (62.5)
Hematuria or hemoglobinuria	2 (40.0)	5 (62.5)
Aplastic anemia	3 (60.0)	1 (12.5)
Renal failure	2 (40.0)	2 (25.0)
Other[a]	0	1 (12.5)
Pre-treatment LDH levels (U/L)		
Median (min, max)	588.50 (444, 2269.7)	251.50 (140.5, 487)

[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.
Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell.

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.

The weight-based dose regimen of ULTOMIRIS provided immediate, complete, and sustained inhibition of terminal complement throughout the entire 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 26-week Primary Evaluation Period in both cohorts. There were no breakthrough hemolysis events in the study 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-naïve cohort and remained stable in the SOLIRIS-experienced cohort during the 26-week Primary Evaluation Period. Sixty percent (3/5) of complement inhibitor-naïve patients and 75% (6/8) of eculizumab-experienced patients achieved haemoglobin stabilisation by Week 26 respectively. Transfusion-avoidance was reached for 84.6% (11/13) of patients during the 26-week Primary Evaluation Period.

These interim efficacy results are presented in table 16 below.

Table 16: Interim Efficacy Outcomes from the Pediatric Study in PNH Patients (ALXN1210-PNH-304) – 26-week primary evaluation period

End Point	**ULTOMIRIS (Naïve, N = 5)**	**ULTOMIRIS (Switch, N = 8)**
LDH - percent change from baseline, Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion avoidance (%), (95% CI)	60.0 (14.66, 94.73)	100.0 (63.06, 100.00)
Hemoglobin stabilization (%), (95% CI)	60.0 (14.66, 94.73)	75 (34.91, 96.81)
Breakthrough hemolysis (%)	0	0

Abbreviations: LDH = lactate dehydrogenase

Based on these data from these interim results, the efficacy of ULTOMIRIS in pediatric PNH patients appears to be similar to that observed in adult PNH patients.

Atypical Hemolytic Uremic Syndrome (aHUS)

Study in Pediatric Patients with aHUS

The pediatric study is a 26-week ongoing, multicenter, single arm, Phase 3 study conducted in pediatric patients.

A total of 21 SOLIRIS-naïve patients with documented diagnosis of aHUS and evidence of TMA were enrolled, of whom 18 were included in the full analysis set. Enrolment criteria excluded patients presenting with TMA due to TTP and STEC-HUS. Two patients were given a single dose, and one patient received 2 doses, but then discontinued and were excluded from the Full Analysis Set because aHUS was not confirmed. The overall mean weight at baseline was 22.2 kg; majority of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (72.2%) had pretreatment extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 33.3% (n = 6) of patients had CKD Stage 5.

A total of 10 patients who switched from SOLIRIS to ULTOMIRIS with documented diagnosis of aHUS and evidence of TMA were enrolled. Patients had to have 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 ravulizumab in patient refractory to eculizumab.

Table 17 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 17: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-312

Parameter	**Statistics**	**Ravulizumab (Naïve, N = 18)**	**Ravulizumab (Switch, N = 10)**
Age at time of first infusion (years) category	n (%)		
Birth to < 2 years		2 (11.1)	1 (10.0)
2 to < 6 years		9 (50.0)	1 (10.0)
6 to < 12 years		5 (27.8)	1 (10.0)
12 to < 18 years		2 (11.1)	7 (70.0)
Sex	n (%)		
Male		8 (44.4)	9 (90.0)
Race[a]	n (%)		
American Indian or Alaskan Native		1 (5.6)	0 (0.0)
Asian		5 (27.8)	4 (40.0)
Black or African American		3 (16.7)	1 (10.0)
White		9 (50.0)	5 (50.0)
Unknown		1 (5.6)	0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelets (10^9/L) blood	Median (min, max)	51.25 (14, 125)	281.75 (207, 415.5)
Hemoglobin (g/L)	Median (min, max)	74.25 (32, 106)	132.0 (114.5, 148)
LDH (U/L)	Median (min, max)	1963.00 (772, 4985)	206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2)	Median (min, max)	22.0 (10, 84)	99.75 (54, 136.5)
Required dialysis at baseline	n (%)	6 (33.3)	0 (0.0)

Note: Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.
Abbreviations: aHUS = atypical hemolytic uremic 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 normalization of hematological parameters (platelet count ≥ 150 x 10^9/L and LDH ≤ 246 U/L) and ≥ 25% improvement in serum creatinine from baseline. 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 14 of the 18 naïve patients (77.8%) during the 26-week Initial Evaluation Period as shown in Table 18.

Table 18: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (ALXN1210-aHUS-312)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	18	14	0.778 (0.524, 0.936)
Components of Complete TMA Response			
Platelet count normalization	18	17	0.944 (0.727, 0.999)
LDH normalization	18	16	0.889 (0.653, 0.986)
≥ 25% improvement in serum creatinine from baseline	18	15	0.833 (0.586, 0.964)
Hematologic normalization	18	16	0.889 (0.653, 0.986)

Note: 1 patient withdrew from study after receiving 2 doses of ravulizumab.

[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 (15 to 97 days). All patients with Complete TMA Response maintained it through the Initial Evaluation Period with continuous improvements seen in renal function. An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 60.50×10^9/L at baseline to 296.67×10^9/L at Day 8 and remained above 296×10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks).

Three additional patients had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period (with a Complete TMA Response occurring at Days 291, 297 and 353); thus, 17 of 18 (94.4%) pediatric patients (95% CI: 72.7%, 99.9%) had a Complete TMA Response. Individual component response increased to 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for each platelet count normalization, 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for LDH normalization, and 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for renal function improvement.

All 6 patients who required dialysis at study entry were able to discontinue dialysis; 5 of which had already done so by Day 43. No patient started dialysis during the study. The majority of the patient population (15/17) improved by 1 or more CKD stages by Day 183; 14 patients improved by 2 or more stages. Table 19 summarizes the secondary efficacy results for Study ALXN1210-aHUS-312.

Table 19: Secondary Efficacy Outcome for Study ALXN1210-aHUS-312

Parameters	Study ALXN1210-aHUS-312 (N = 18)	
Hematologic 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		

Parameters	Study ALXN1210-aHUS-312 (N = 18)	
Mean (SD) Median	262.41 (59.995) 247.00	-2044.13 (1328.059) -1851.50
Increase in hemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period m/N proportion (95% CI)*	 16/18 0.889 (0.653, 0.986)	
CKD stage shift from baseline, Day 183 Improved[a] m/n Proportion (95% CI)* Worsened[b] m/n Proportion (95% CI)*	 15/17 0.882 (0.636, 0.985) 0/11 0.000 (0.000, 0.285)	
eGFR (mL/min/1.73 m^2), Day 183 Mean (SD) Median	Observed value (n=17) 108.5 (56.87) 108.0	Change from baseline (n=17) 85.4 (54.33) 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.
*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper Pearson method.
[a] Improved excludes patients with Stage 1 at baseline, as they cannot improve; [b] Worsened excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

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

The efficacy of ravulizumab for the treatment of aHUS appears similar in paediatric and adult patients.

5.2 Pharmacokinetic properties

Absorption

ULTOMIRIS doses are 100% bioavailable resulting from intravenous administration. The time to maximum observed concentration (t_{max}) is expected at the end of infusion (EOI) or soon after EOI. Over the studied dose and regimen range, ravulizumab 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 pediatric patients with PNH or complement mediated-TMA treated with ravulizumab IV, adult patients with gMG treated with ravulizumab IV, are presented in Table 20.

Biotransformation and Elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized 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 contains only natural occurring amino acids and has no known active metabolites. The mean (SD) terminal elimination half-life and clearance of ravulizumab in adult and pediatric patients with PNH or complement-mediated TMA treated with ravulizumab IV, adult patients with gMG treated with ravulizumab IV are presented in Table 20.

Pharmacokinetic Parameters

A linear, 2-compartment PK model was developed that adequately described the observed ravulizumab PK following intravenous and subcutaneous administration. The estimated mean (SD) clearance, central volume, volume at steady state and terminal elimination half-life following multiple dosing of ravulizumab in adult and pediatric patients with PNH or complement-mediated TMA treated with ravulizumab IV, adult patients with gMG treated with ravulizumab IV are presented in Table 20.

Table 20: Estimated Central Volume, Distribution, Biotransformation and Elimination Parameters Following ULTOMIRIS Treatment

	Adult Patients with PNH	**Adult and Pediatric Patients with PNH**	**Adult and Pediatric Patients with Complement-Mediated TMA**	**Adult Patients with gMG**
Estimated central volume (liters) Mean (SD)	3.44 (0.66)	Adults: 3.44 (0.66) Pediatrics: 2.87 (0.60)	Adults: 3.25 (0.61) Pediatrics: 1.14 (0.51)	3.42 (0.756)
Volume of distribution at steady state (liters) Mean (SD)	5.35 (0.92)	5.30 (0.9)	5.22 (1.85)	5.74 (1.16)
Terminal elimination half-life (days) Mean (SD)	49.7 (9.0)	49.6 (9.1)	51.8 (16.2)	56.6 (8.36)
Clearance (liters/day) Mean (SD)	0.08 (0.022)	0.08 (0.022)	0.08 (0.04)	0.08 (0.02)

Therapeutic concentrations are achieved immediately following the first dose of ULTOMIRIS. In patients with PNH, complement-mediated TMA, gMG pharmacodynamic activity correlates directly with ravulizumab serum concentrations above the target exposure level and results in free C5 levels < 0.5 μg/mL, achieving immediate, complete and sustained terminal complement inhibition in all patients.

PK parameters for ULTOMIRIS are consistent across PNH, complement-mediated TMA, gMG patient populations.

Special Populations

No formal trial of the effect of sex, race, age (geriatric), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on population-PK assessment, no impact of sex, age, race and hepatic or renal function on ravulizumab PK was identified in patients with PNH, complement-mediated TMA, or gMG and as a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab have been studied in complement-mediated TMA patients with a range of renal impairment and age including patients receiving dialysis. There have been no observed differences in pharmacokinetic parameters noted in these subpopulations including patients with proteinuria.

Body weight is a clinically significant covariate on the pharmacokinetics of ravulizumab.

5.3 Preclinical safety data

The tissue cross-reactivity of ravulizumab was evaluated by assessing binding to a panel of human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression. No unexpected tissue cross-reactivity was observed.

In a 26-week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. C5-induced hemolytic activity in an ex vivo assay was effectively blocked throughout the course of the study in both female and male mice.

Animal reproductive toxicology studies have not been conducted with ravulizumab, but were conducted in mice with a murine surrogate complement inhibitory antibody, BB5.1. No clear treatment-related effects or adverse effects were observed in the murine surrogate reproductive toxicology studies in mice. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human ravulizumab dose, based on a body weight comparison); however, the exposure did not increase fetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of ravulizumab.

Non-clinical data reveal no special hazard for humans based on nonclinical studies using a murine surrogate molecule, BB5.1, in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ULTOMIRIS 300 mg/3 mL and 1100 mg/11 mL (100 mg/mL)

Sodium phosphate, monobasic
Sodium phosphate, dibasic
Polysorbate 80
L-arginine
Sucrose
Water for injection

ULTOMIRIS 100 mg/mL contains 4.6 mg of sodium per 3 mL vial or 16.8 mg 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.

ULTOMIRIS should only be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection as diluent.

6.3 Shelf life

Please refer to expiry date on outer carton.

After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product using ULTOMIRIS 100 mg/mL have been demonstrated for up to 24 hours at 2°C – 8°C (36°F – 46°F) and up to 4 hours at room temperature.

6.4 Special precautions for storage

ULTOMIRIS vials must be stored under refrigerated conditions at 2°C – 8°C (36°F – 46°F). Do not freeze.

Vials must not be shaken.

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

For storage conditions after dilution of the 100 mg/mL medicinal product see Section 6.3.

6.5 Nature and contents of container

Intravenous Use

Pack size of one vial per carton.

ULTOMIRIS 300 mg/3 mL and 1100 mg/11 mL (100 mg/mL)

3 mL of sterile concentrate in a vial (Type I glass) with a stopper and a seal.
11 mL of sterile concentrate in a vial (Type I glass) with a stopper and a seal.

Not all pack sizes may be marketed.

Product Owner

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7. INSTRUCTION FOR USE

Each vial of ULTOMIRIS is intended for single use only.

7.1 Intravenous use

ULTOMIRIS 100 mg/mL requires dilution to a final concentration of 50 mg/mL.

Aseptic technique must be used.

Prepare ULTOMIRIS as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see Section 4.2.
2. 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.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 50 mg/mL for ULTOMIRIS 100 mg/mL.
5. The prepared solution should be administered immediately following preparation. Do not administer as an intravenous push or bolus injection. Refer to the administration reference Table 4 and Table 5 in Section 4.2 for minimum infusion duration. Infusion must be administered through a 0.2 μm filter.
6. If the medicinal product is not used immediately after reconstitution, storage times at 2°C – 8°C (36°F – 46°F) must not exceed 24 hours taking into account the expected infusion time.

The loading, maintenance, and supplemental dose administration reference tables for ULTOMIRIS 100 mg/mL are provided in Table 21, Table 22 and Table 23, respectively.

Table 21: Loading Dose Administration Reference Table for ULTOMIRIS 100 mg/mL

Body Weight Range (kg) [a]	**Loading dose (mg)**	**ULTOMIRIS volume (mL)**	**Volume of NaCl diluent[b] (mL)**	**Total volume (mL)**
≥ 5 to < 10*	600	6	6	12
≥ 10 to < 20*	600	6	6	12
≥ 20 to < 30*	900	9	9	18
≥ 30 to < 40*	1200	12	12	24
≥ 40 to < 60	2400	24	24	48
≥ 60 to < 100	2700	27	27	54
≥ 100	3000	30	30	60

* For PNH and aHUS indications only.

[a] Body weight at time of treatment.

[b] ULTOMIRIS should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

Table 22: Maintenance Dose Administration Reference Table for ULTOMIRIS 100 mg/mL

Body Weight Range (kg) [a]	Maintenance dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 5 to < 10*	300	3	3	6
≥ 10 to < 20*	600	6	6	12
≥ 20 to < 30*	2100	21	21	42
≥ 30 to < 40*	2700	27	27	54
≥ 40 to < 60	3000	30	30	60
≥ 60 to < 100	3300	33	33	66
≥ 100	3600	36	36	72

* For PNH and aHUS indications only.
[a] Body weight at time of treatment.
[b] ULTOMIRIS should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

Table 23: Supplemental Dose Administration Reference Table for ULTOMIRIS 100 mg/mL

Body Weight Range (kg) [a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 40 to < 60	600	6	6	12
	1200	12	12	24
	1500	15	15	30
≥ 60 to < 100	600	6	6	12
	1500	15	15	30
	1800	18	18	36
≥ 100	600	6	6	12
	1500	15	15	30
	1800	18	18	36

[a] Body weight at time of treatment.
[b] ULTOMIRIS should be only diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.