SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 100 mg/ml

Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultomiris is a formulation of ravulizumab, produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

Ultomiris 300 mg/3 mL concentrate for solution for infusion

Each vial of 3 mL contains 300 mg of ravulizumab (100 mg/mL).
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Excipient(s) with known effect:
Sodium (4.6 mg per 3 mL vial), polysorbate 80 (1.5 mg per vial)

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

Each vial of 11 mL contains 1,100 mg of ravulizumab (100 mg/mL).
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Excipient(s) with known effect:
Sodium (16.8 mg per 11 mL vial), polysorbate 80 (5.5 mg per vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Translucent, clear to yellowish colour, pH 7.4 solution and osmolality of approximately 250 – 350 mOsm/kg..

Patient safety information card
The marketing of Ultomiris is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paroxysmal nocturnal haemoglobinuria (PNH)
Ultomiris is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with PNH:
- in patients with haemolysis with clinical symptom(s) indicative of high disease activity

- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Atypical haemolytic uremic syndrome (aHUS)
Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

Generalized myasthenia gravis (gMG)
Ultomiris is indicated in the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.

Neuromyelitis optica spectrum disorder (NMOSD)
Ultomiris is indicated in the treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive (see section 5.1).

4.2 Posology and method of administration

Ravulizumab must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological, renal, neuromuscular, or neuroinflammatory disorders.

Posology

Adult patients with PNH, aHUS, gMG or NMOSD
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. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab), but the subsequent dose should be administered according to the original schedule.

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

Table 1: Ravulizumab weight-based dosing regimen for adult patients with body weight greater than or equal to 40 kg

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 40 to < 60	2,400	3,000	Every 8 weeks
≥ 60 to < 100	2,700	3,300	Every 8 weeks
≥ 100	3,000	3,600	Every 8 weeks

*First maintenance dose is administered 2 weeks after 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 2).

Table 2: Supplemental Dose of Ultomiris after PE, PP, or IVIg

Body Weight Range (kg)	**Most Recent ULTOMIRIS Dose (mg)**	**Supplemental Dose (mg) following each PE or PP Intervention**	**Supplemental Dose (mg) following Completion of an IVIg Cycle**
≥ 40 to < 60	2,400	1,200	600
	3,000	1,500	
≥ 60 to < 100	2,700	1,500	600
	3,300	1,800	
≥ 100	3,000	1,500	600
	3,600	1,800	
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; kg = kilogram; PE = plasma exchange; PP = plasmapheresis

PNH is a chronic disease and treatment with ravulizumab is recommended to continue for the patient's lifetime, unless the discontinuation of ravulizumab is clinically indicated (see section 4.4).

In aHUS, ravulizumab treatment to resolve thrombotic microangiopathy (TMA) manifestations should be for 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 (see section 4.4).

In patients with gMG or NMOSD, treatment with ravulizumab has only been studied in the setting of chronic administration (see section 4.4).

Ravulizumab has not been studied in gMG patients with an MGFA Class V.

Special populations

Elderly
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 a geriatric population – although experience with ravulizumab in elderly patients with PNH, aHUS or NMOSD in clinical studies is limited.

Renal impairment
No dose adjustment is required for patients with renal impairment, see section 5.2.
Hepatic impairment
The safety and efficacy of ravulizumab have not been studied in patients with hepatic impairment; however pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment.

Paediatric population
Paediatric patients with PNH and aHUS with body weight ≥ 40 kg are treated in accordance with the adult dosing recommendations (Table 1). The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg are shown in Table 3.

For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses should be administered per weight-based dosing regimen shown in Table 3, starting 2 weeks after loading dose administration.

Table 3: Ravulizumab weight-based dosing regimen for paediatric patients with PNH or aHUS below 40 kg

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 10 to < 20	600	600	Every 4 weeks
≥ 20 to < 30	900	2,100	Every 8 weeks
≥ 30 to < 40	1200	2,700	Every 8 weeks

*First maintenance dose is administered 2 weeks after loading dose

Data to support safety and efficacy of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in section 4.8 but no recommendation on a posology can be made for patients below 10 kg body weight.

Ravulizumab has not been studied in paediatric patients with PNH who weigh less than 30 kg. The posology of ravulizumab for paediatric patients less than 30 kg is based on the posology used for paediatric patients with aHUS, on the basis of the pharmacokinetic/pharmacodynamic (PK/PD) data available in aHUS and PNH patients treated with ravulizumab.

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

Method of administration

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

Ultomiris concentrate for solution for infusion is presented as 3 mL and 11 mL vials and must be diluted to a final concentration of 50 mg/mL. Following dilution, Ultomiris is to be administered by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 0.17 to 1.3 hours (10 to 75 minutes) depending on body weight (see Table 4 and Table 5 below).

Table 4: Dose administration rate for Ultomiris

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
≥ 10 to < 20[b]	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30[b]	900	35 (0.6)	2,100	75 (1.3)
≥ 30 to < 40[b]	1,200	31 (0.5)	2,700	65 (1.1)
≥ 40 to < 60	2,400	45 (0.8)	3,000	55 (0.9)
≥ 60 to < 100	2,700	35 (0.6)	3,300	40 (0.7)
≥ 100	3,000	25 (0.4)	3,600	30 (0.5)

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

Table 5: Dose administration rate for supplemental doses of Ultomiris

Body weight range (kg)[a]	Supplemental dose [b] (mg)	Minimum infusion duration minutes (hours)
≥ 40 to < 60	600	15 (0.25)
	1,200	25 (0.42)
	1,500	30 (0.5)
≥ 60 to < 100	600	12 (0.20)
	1,500	22 (0.36)
	1,800	25 (0.42)
≥ 100	600	10 (0.17)

	1,500	15 (0.25)
	1,800	17 (0.28)

[a] Body weight at time of treatment.
[b] Refer to Table 2 for selection of ravulizumab supplemental dose

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation (see section 4.4).
- 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 precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Serious meningococcal infection

Due to its mechanism of action, the use of ravulizumab increases the patient's susceptibility to meningococcal infection/sepsis (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur (see section 4.8). To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to initiating ravulizumab unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. Patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against all available serogroups including A, C, Y, W135 and B, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use. If the patient is being switched from eculizumab treatment, physicians should verify that meningococcal vaccination is current according to national 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. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with ravulizumab and in patients treated with 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 guide and a Patient card.

Immunisation

Prior to initiating ravulizumab therapy, it is recommended that patients initiate immunisations according to current immunisation guidelines.

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 strictly need to adhere to the national vaccination recommendations for each age group.

Other systemic infections

Ravulizumab therapy should be administered with caution to patients with active systemic infections. Ravulizumab blocks terminal complement activation; therefore, patients may have increased susceptibility to infections caused by *Neisseria* species and encapsulated bacteria. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.
Patients should be provided with information from the Package Information Leaflet to increase their awareness of potential serious infections and their signs and symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion-related reactions

Administration of ravulizumab may result in systemic infusion-related reactions and allergic or hypersensitivity reactions, including anaphylaxis (see section 4.8).
In case of systemic infusion-related reaction, if signs of cardiovascular instability or respiratory compromise occur, administration of ravulizumab should be interrupted and appropriate supportive measures should be instituted.

Treatment discontinuation for PNH

If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of serious intravascular haemolysis, identified by elevated LDH (lactate dehydrogenase) levels 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 ravulizumab 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 ravulizumab.

Treatment discontinuation for aHUS

There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) 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:

- At least 2 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)

Or

- 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, reinitiation of ravulizumab treatment should be considered, beginning with the loading dose and maintenance dose (see section 4.2).

Treatment discontinuation for gMG

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

Treatment discontinuation for NMOSD

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

Switch from eculizumab to ravulizumab

In gMG patients who are not responding to eculizumab approved dosing regimen, treatment with ravulizumab is not recommended.

Sodium content

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 0.18 g sodium per 72 mL at the maximal dose, equivalent to 9.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Polysorbate 80 content

This medicinal product contains 1.5 mg of polysorbate 80 in each 3 mL vial and 5.5 mg in each 11 mL vial, which is equivalent to 0.53 mg/kg or less at the maximum dose for adult patients and paediatric patients with body weight more than 10 kg. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the potential inhibitory effect of ravulizumab on complement-dependent cytotoxicity of rituximab, ravulizumab may reduce the expected pharmacodynamic effects of rituximab.

Chronic intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as ravulizumab and thereby decrease serum ravulizumab concentrations.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no clinical data from the use of ravulizumab in pregnant women.
Nonclinical reproductive toxicology studies were not conducted with ravulizumab (see section 5.3).
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 immunoglobulin G (IgG) are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the foetal circulation.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

In pregnant women the use of ravulizumab may be considered following an assessment of the risks and benefits.

Breast-feeding

It is unknown whether ravulizumab is excreted into human milk. 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.

A risk to infants cannot be excluded.
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 with ravulizumab and for 8 months after treatment.

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.

4.7 Effects on ability to drive and use machines

Ultomiris has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with ravulizumab are headache (30.6%), upper respiratory tract infection (21.6%), nasopharyngitis (20.4%), diarrhoea (18.7%), pyrexia (17.7%), nausea (15%), arthralgia (14.4%), back pain (13.6%), fatigue (13.3%), abdominal pain (12.3%), dizziness (10.7%) and urinary tract infection (10.7%). The most serious adverse reactions are meningococcal infection (0.7%) including meningococcal sepsis, meningococcal meningitis, encephalitis meningococcal, meningococcal infection (see section 4.4) and disseminated gonococcal infection (0.2%) including disseminated gonococcal infection and gonococcal infection.

Tabulated list of adverse reactions

Table 6 gives the adverse reactions observed from clinical trials and from post-marketing experience.
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 6: Adverse Drug reactions from clinical trials and postmarketing experience

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]
Immune system disorders		Hypersensitivity [e]	Anaphylactic reaction [d]
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

[d] Estimated from postmarketing experience

[e] Hypersensitivity is a group term for Preferred Term drug hypersensitivity with related causality and Preferred Term hypersensitivity

Description of selected adverse reactions

Meningococcal infection/sepsis/encephalitis
Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, < 1 % of patients developed serious meningococcal infections while receiving treatment with ravulizumab; all were adult patients with PNH or NMOSD who had been vaccinated. Please refer to section 4.4 for information on prevention and treatment of suspected meningococcal infection. In patients treated with ravulizumab, meningococcal infections 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.

Infusion-related reactions
In clinical trials, infusion-related reactions were common (≥1%). These events, which were mild to moderate in severity and transient, included back pain, abdominal pain, muscle spasms, drop in blood pressure, elevation in blood pressure, rigors, limb discomfort, hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ravulizumab.

Immunogenicity
In adult PNH patient studies (N = 475), a paediatric PNH study (N = 13), aHUS studies (N=89), a gMG study (N=86) and an NMOSD study (N = 58), 2 (0.3 %) cases of development of treatment-emergent anti-drug antibody have been reported with ravulizumab (1 adult patient with PNH and 1 adult patient with aHUS). These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

Paediatric population
Paroxysmal nocturnal haemoglobinuria (PNH)
In paediatric PNH patients (N=13, aged 9 to 17 years old) enrolled in the paediatric PNH Study (ALXN1210-PNH-304), the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reactions reported in paediatric PNH patients were abdominal pain, nausea, nasopharyngitis and headache, which occurred in 3 patients (23.1%).

Atypical haemolytic uremic syndrome (aHUS)
In paediatric patients with evidence of aHUS (N=34, aged 10 months to less than 18 years) included in ALXN1210-aHUS-312 study, the safety profile of ravulizumab appeared similar to that observed in adult patients with evidence of aHUS. The safety profiles in the different paediatric subsets of age appear similar. The safety data for patient below 2 years of age is limited to four patients. The most common adverse reactions (≥ 20%) reported in paediatric patients were pyrexia, vomiting, diarrhoea, headache, nasopharyngitis, upper respiratory tract infection and abdominal pain.

Generalized myasthenia gravis (gMG)
Ravulizumab has not been studied in paediatric patients with gMG.

Neuromyelitis optica spectrum disorder (NMOSD)
Ravulizumab has not been studied in paediatric patients with NMOSD.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ02

Mechanism of action

Ravulizumab is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the complement protein C5, 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. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Pharmacodynamic effects

Following ravulizumab treatment in both adult and paediatric complement-inhibitor naïve patients and eculizumab-experienced patients with PNH in Phase 3 studies, immediate, complete and sustained 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. Immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS, in adult patients with gMG and in adult patients with NMOSD by the end of the first infusion and throughout the primary treatment period.
The extent and duration of the pharmacodynamic response in patients with PNH, aHUS, gMG , or NMOSD were exposure dependent for ravulizumab. Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition. In gMG, terminal complement activation leads to MAC deposition at the neuromuscular junction and impairment of neuromuscular transmission. In NMOSD, terminal complement activation leads to MAC formation and C5a-dependent inflammation, astrocyte necrosis, and damage to surrounding glial cells and neurons.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria (PNH)
The safety and efficacy of ravulizumab 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,
- an eculizumab -experienced study in adult patients with PNH who were clinically stable after having been treated with eculizumab for at least the previous 6 months.

Ravulizumab was dosed in accordance with the recommended dosing described in section 4.2 (4 infusions of ravulizumab over 26 weeks) while eculizumab was administered according to the approved dosing regimen of eculizumab 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 ravulizumab or eculizumab, 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 ravulizumab and eculizumab treatment groups in either of the Phase 3 studies. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 studies.

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

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 ravulizumab. 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**	**Ravulizumab (N = 125)**	**Eculizumab (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)
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 Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[b]	n (%)	121 (96.8) 103 (82.4) 81 (64.8) 41 (32.8) 19 (15.2) 7 (5.6) 3 (2.4) 27 (21.6)	120 (99.2) 105 (86.8) 75 (62.0) 38 (31.4) 11 (9.1) 6 (5.0) 4 (3.3) 13 (10.7)

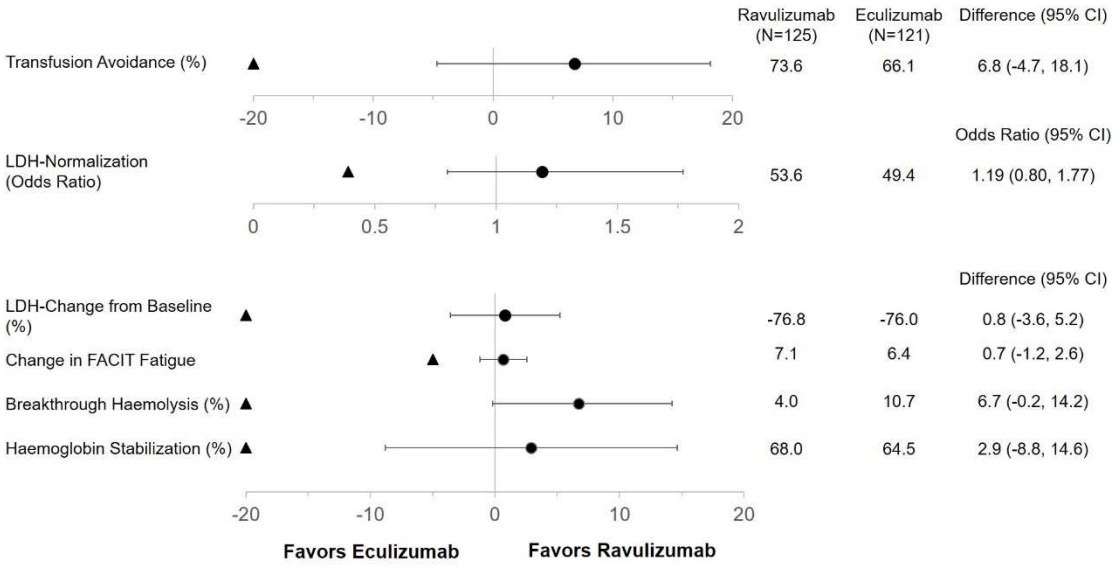
[a] Based on medical history.

[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 haemolysis as directly measured by normalisation 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 haemolysis and proportion of patients with stabilised haemoglobin.

Ravulizumab 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 black dots indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

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

Study in adult PNH patients previously treated with eculizumab (ALXN1210-PNH-302)

The eculizumab-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 (LDH ≤ 1.5 x ULN) after having been treated with eculizumab for at least the past 6 months and was followed by a long-term extension period where all patients received ravulizumab.

PNH medical history was similar between ravulizumab and eculizumab treatment groups. The 12-month transfusion history was similar between ravulizumab and eculizumab 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 eculizumab-experienced study, with no apparent clinically meaningful differences observed between the treatment arms.

Table 8: Baseline characteristics in the eculizumab-experienced study

Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (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)
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 Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[b]	n (%)	90 (92.8) 64 (66.0) 47 (48.5) 34 (35.1) 11 (11.3) 3 (3.1) 4 (4.1) 14 (14.4)	96 (98.0) 67 (68.4) 48 (49.0) 39 (39.8) 7 (7.1) 6 (6.1) 9 (9.2) 14 (14.3)

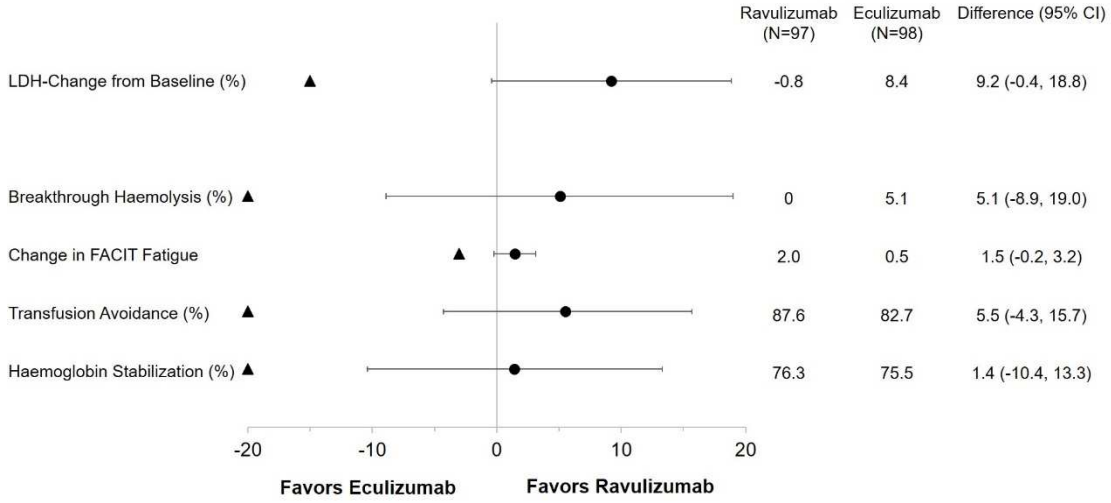
[a] Based on medical history.

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

The primary endpoint was 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 (TA), and proportion of patients with stabilised haemoglobin.

Ravulizumab 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 (eculizumab-experienced study)



Note: The black triangle indicates the non-inferiority margins, and black dot indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval.

The final efficacy analysis for the study included all patients ever treated with ravulizumab (n=192) and had a median treatment duration of 968 days. The final analysis confirmed that ravulizumab treatment responses observed during the primary evaluation period were maintained throughout the duration of the study.

Atypical haemolytic uremic syndrome (aHUS)

Study in adult patients with aHUS (ALXN1210-aHUS-311)

The adult study was a multicentre, 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 patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related haemolytic uremic syndrome (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. 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 Asian White Unknown/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)
Haemoglobin (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: 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 ≥ 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 for 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 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 ravulizumab, increasing from 118.52 × 10^9/L at baseline to 243.54 × 10^9/L at Day 8 and remaining above 227 × 109/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).

Over two thirds of the patient population who were mostly CKD Stage 4 or 5 at baseline improved by 1 or more CKD stages by Day 743 of study. Improvement in renal function as

measured by eGFR continued to be stable through end of study. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week initial evaluation period.

Of the 27 patients who did not require dialysis at study entry, 19 patients remained off dialysis during the entire study period and 8 patients initiated dialysis during the study, with 2 of these patients discontinuing dialysis during the study. One of the patients that discontinued dialysis during the extension study period, then reinitiated dialysis and continued through study completion.

Table 11: Secondary efficacy outcome for the 26- Week Initial Evaluation Period of study ALXN1210-aHUS-311

Parameters	**Study ALXN1210-aHUS-311 (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		
n/m	40/56	
proportion (95% CI)*	0.714 (0.587, 0.842)	
CKD stage shift from baseline, Day 183		
Improved[a]		
n/m	32/47	
Proportion (95% CI)*	0.681 (0.529, 0.809)	
Worsened[b]		
n/m	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.

The final efficacy analysis for the study on all patients treated with ravulizumab over a median treatment duration of 130.36 weeks confirmed that ravulizumab treatment responses observed during the Primary Evaluation Period were maintained throughout the duration of the study.

Generalized Myasthenia Gravis (gMG)

Study in adult patients with gMG

The efficacy and safety of ravulizumab in adult patients with gMG was assessed in a Phase 3, randomised, double-blind, placebo-controlled, multicentre study (ALXN1210-MG-306). Patients participating in this study were subsequently allowed to enter an Open-Label Extension Period during which all patients received ravulizumab.

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 randomised to receive either ravulizumab (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 Randomised-Controlled Period 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)**	**Ravulizumab (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) (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	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 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 was 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 assessing 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.

Ravulizumab 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)**	**Ravulizumab (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 Randomised-Controlled Period.

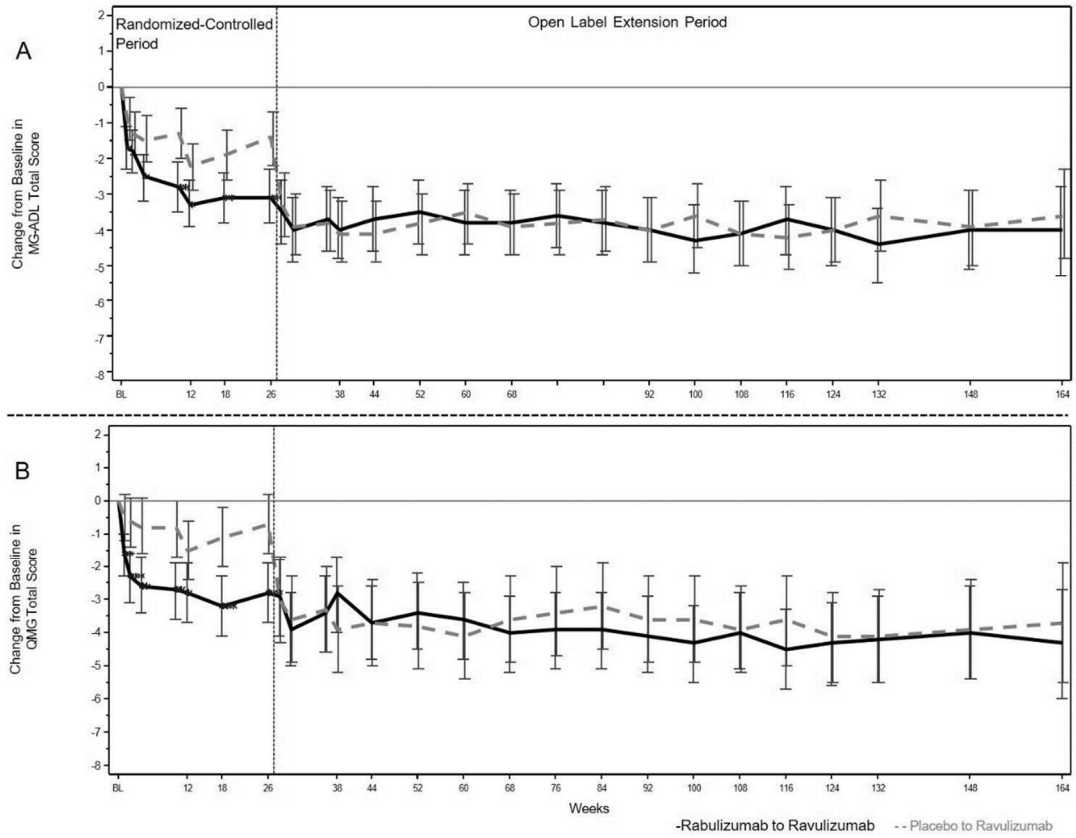
Table 14: Clinical deterioration and rescue therapy

Variable	Statistic	Placebo (N = 89)	Ravulizumab (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.

In patients who initially received Ultomiris during the Randomised-Controlled Period and continued to receive Ultomiris up to 164-weeks of the Open-Label Extension Period, the treatment effect continued to be sustained (Figure 3). In patients who initially received placebo during the 26-week Randomised-Controlled Period and initiated treatment with Ultomiris during the Open-Label Extension Period, a rapid and sustained treatment response on all endpoints including MG-ADL and QMG (Figure 3), was observed over a median treatment duration of approximately 2 years.

Figure 3: 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: Randomized 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

In the Open-Label Extension Period of the study, clinicians had the option to adjust immunosuppressant therapies. At the end of the Open-Label Extension Period (median duration of Ultomiris treatment both during Randomised-Control Period and Open-Label Extension was 759 days), 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 ravulizumab treatment.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Study in adult patients with NMOSD

The efficacy of ravulizumab 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 53.4% of patients were on ravulizumab monotherapy. Patients on selected ISTs (i.e., corticosteroids, azathioprine, mycophenolate mofetil, tacrolimus) were permitted to continue on therapy in combination with ravulizumab, 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 15.

Table 15: Patient disease history and baseline characteristics in study ALXN1210-NMO-307

Variable	**Statistic**	**ALXN1210-NMO-307 Ravulizumab (N = 58)**
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Mean (SD)	5.2 (6.38)
	Median	2.0
	Min, max	0.19, 24.49
Historical ARR within 24 months prior to screening	Mean (SD)	1.87 (1.59)
	Median	1.44
	Min, max	0.5, 6.9
Baseline HAI score	Mean (SD)	1.2 (1.42)
	Median	1.0
	Min, max	0, 7
Baseline EDSS score	Mean (SD)	3.30 (1.58)
	Median	3.25
	Min, max	0.0, 7.0
Any historical rituximab use	n (%)	21 (36.2)
Number of patients receiving stable corticosteroids only at study entry	n (%)	11 (19.0)
Number of patients not receiving any IST at study entry	n (%)	31 (53.4)

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

In the final efficacy analysis with median follow up of 170.29 weeks, no adjudicated on-trial relapses were observed in ravulizumab treated patients through the end of study. Ravulizumab treatment responses observed during the Primary Evaluation Period were maintained throughout the duration of the study. In addition, among the 27 patients on IST treatment at Baseline, 17 (63%) had a decrease or stopped at least one IST therapy during treatment with ravulizumab.

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

Paediatric population

Paroxysmal nocturnal haemoglobinuria (PNH)

Study in paediatric patients with PNH (ALXN1210-PNH-304)
The paediatric study (ALXN1210-PNH-304) is a multicentre, open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor-naïve paediatric patients with PNH.
From interim results, a total of 13 PNH paediatric patients completed ravulizumab treatment during the primary evaluation period (26 weeks) of Study ALXN1210-PNH-304. Five of the 13 patients had never been treated with a complement inhibitor and 8 patients received treatment with eculizumab prior to study entry.
Most of the patients were between 12 years and 17 years of age at first infusion (mean: 14.4 years), with 2 patients under 12 years old (11 years 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 16 presents the baseline disease history and characteristics of the paediatric patients enrolled in Study ALXN1210-PNH-304.

Table 16: 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 (%) Median (min, max)	(N = 4) 40.05 (6.9, 68.1)	(N = 6) 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 Median (min, max)	10 5.0 (4, 6)	2 1.0 (1, 1)
Units of pRBC/whole blood transfused within 12 months prior to first dose Total Median (min, max)	14 7.0 (3, 11)	2 2.0 (2, 2)
Patients with any PNH-associated conditions prior to informed consent, n (%) Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Other[a]	5 (100) 2 (40.0) 2 (40.0) 3 (60.0) 2 (40.0) 0	8 (100) 5 (62.5) 5 (62.5) 1 (12.5) 2 (25.0) 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 haemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell.

Based on body weight, patients received a loading dose of ravulizumab 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 eculizumab therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of eculizumab.

The weight-based dose regimen of ravulizumab provided immediate, complete, and sustained inhibition of terminal complement throughout the 26-week primary evaluation period regardless of prior experience with eculizumab. Following initiation of ravulizumab treatment, steady-state therapeutic serum concentrations of ravulizumab were achieved immediately after the first dose and maintained throughout the 26-week primary evaluation period in both cohorts. There were no breakthrough haemolysis 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 eculizumab-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 by 84.6% (11/13) of patients during the 26-week primary evaluation period.
These interim efficacy results are presented in Table 17 below.

Table 17: Efficacy outcomes from the paediatric study in PNH patients (ALXN1210-PNH-304) - 26-week primary evaluation period

End Point	**Ravulizumab (Naïve, N = 5)**	**Ravulizumab (Switch, 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

Long term efficacy results through end of study over a median treatment duration of 915 days resulted in a sustained treatment response in paediatric patients with PNH.

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

Atypical Haemolytic Uremic Syndrome (aHUS)

Use of Ultomiris in paediatric patients for treatment of aHUS is supported by evidence from one paediatric clinical study (a total of 31 patients with documented aHUS were enrolled; 28 patients aged 10 months to 17 years were included in the full analysis set).

Study in Paediatric Patients with aHUS (ALXN1210 aHUS 312)

The paediatric study was a 26-week, multicentre, single arm, Phase 3 study conducted in paediatric patients and patients were allowed to enter an extension period for up to 4.5 years.

A total of 24 eculizumab-naïve patients with documented diagnosis of aHUS and evidence of TMA were enrolled, of which 20 were included in the full analysis set. 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 then discontinued and were excluded from the Full Analysis Set because aHUS eligibility was not confirmed. The overall mean weight at baseline was 21.2 kg; majority of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (70.0%) had pretreatment 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 eculizumab to ravulizumab, had documented diagnosis of aHUS and evidence of TMA were enrolled. Patients had to have clinical response to eculizumab 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 18 presents the baseline characteristics of the paediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 18: Demographics and baseline characteristics in study ALXN1210-aHUS-312

Parameter	**Statistics**	**Ravulizumab (Naïve, N = 20)**	**Ravulizumab (Switch, N = 10)**
Age at time of first infusion (years) category	n (%)		
Birth to < 2 years		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	n (%)		
Male		8 (40.0)	9 (90.0)
Race[a]	n (%)		
American Indian or Alaskan Native		1 (5.0)	0 (0.0)
Asian		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)
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)
Haemoglobin (g/L)	Median (min, max)	74.25 (32, 106)	132.0 (114.5, 148)
LDH (U/L)	Median (min, max)	1963.0 (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 (%)	7 (35.0)	0 (0.0)

Note: Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.
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 ≥ 150 x 10^9/L and LDH ≤246 U/L) and ≥ 25% improvement in serum creatinine from baseline in eculizumab-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 19.

Table 19: 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	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)

[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 99 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 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 at Days 295 for 2 patients and Day 351 for 1 patient. resulting in the achievement of Complete TMA response in 18 of 20 paediatric patients (90%; 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 for platelet count normalisation, 19 of 20 (95.0%; 95% CI: 75.1%, 99.9%) patients for LDH normalisation, and in 18 of 20 (90.0%; 95% CI: 68.3%, 98.8%) patients for renal function improvement.

All 7 of the 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 chronic kidney disease (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. Improvement in renal function as measured by eGFR continued to be stable through end of study. Table 20 summarises the secondary efficacy results for Study ALXN1210-aHUS-312.

Table 20: Secondary efficacy outcome for the 26-Week Initial Evaluation Period for study ALXN1210-aHUS-312

Parameters	Study ALXN1210-aHUS-312 (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		
n/m	17/20	
proportion (95% CI)*	0.850 (0.621, 0.968)	

Parameters	Study ALXN1210-aHUS-312 (N=20)	
CKD stage shift from baseline, Day 183		
Improved[a]		
n/m	15/17	
Proportion (95% CI)*	0.882 (0.636, 0.985)	
Worsened[b]		
n/m	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	80.0

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 eculizumab-experienced patients, switching to ravulizumab 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.
The final efficacy analysis for the study on all paediatric patients treated with ravulizumab over a median treatment duration of 130.60 weeks confirmed that ravulizumab treatment responses observed during the Primary Evaluation Period were maintained throughout the duration of the study

Generalized Myasthenia Gravis (gMG)

See 4.2 for information on paediatric use.

Neuromyelitis optica spectrum disorder (NMOSD)

See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Because the route of administration is an intravenous infusion and the pharmaceutical form is a solution, 100 % of the administered dose of ravulizumab is considered bioavailable. The time to maximum observed concentration (t_{max}) is expected at the end of infusion (EOI) or soon after EOI. Therapeutic steady-state drug concentrations are reached after the first dose.

Distribution

The mean (standard deviation [SD]) central volume and volume of distribution at steady state for adult and paediatric patients with PNH or aHUS, and adult patients with gMG or NMOSD are presented in Table 21.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab 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 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 in adult and paediatric patients with PNH, adult and paediatric patients with aHUS and adult patients with gMG or NMOSD are presented in Table 21.

Table 21: Estimated central volume, distribution, biotransformation, and elimination parameters following ravulizumab administration

	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)

Abbreviations: aHUS = atypical haemolytic uremic syndrome; gMG = generalised myasthenia gravis; NMOSD = neuromyelitis optica spectrum disorder; PNH = paroxysmal nocturnal haemoglobinuria; SD = standard deviation.

Linearity/non-linearity

Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear pharmacokinetics (PK).

Special populations

Weight
Body weight is a significant covariate in patients with PNH, aHUS, gMG, or NMOSD resulting in lower exposures in heavier patients. Weight-based dosing is proposed in section 4.2, Table 1, Table 2 and Table 3.

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 the studied healthy volunteers, subjects and patients with PNH, aHUS, gMG, or NMOSD and as a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab 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 subpopulations of patients including patients with proteinuria.

5.3 Preclinical safety data

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 foetal 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 1,100 mg/11 mL concentrates for solution for infusion
Sucrose
Sodium phosphate monobasic
Sodium phosphate dibasic
L-Arginine
Polysorbate 80
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Dilution should only use sodium chloride 9 mg/mL (0.9 %) solution for injection as diluent.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C)
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack size of one vial.

Ultomiris 300 mg/3 mL concentrate for solution for infusion

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

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

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

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only.

This medicinal product requires dilution to a final concentration of 50 mg/mL.

Aseptic technique must be used.

Prepare Ultomiris concentrate for solution for infusion 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.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2 °C-8 °C. If stored at 2 °C-8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to the Table 4 and Table 5 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C – 8 °C or 4 hours at room temperature taking into account the expected infusion time.

Table 22: Loading dose administration reference table for Ultomiris

Body weight range (kg)[a]	**Loading dose (mg)**	**Ultomiris volume (mL)**	**Volume of NaCl diluent[b] (mL)**	**Total volume (mL)**
≥ 10 to < 20	600	6	6	12
≥ 20 to < 30	900	9	9	18
≥ 30 to < 40	1,200	12	12	24
≥ 40 to < 60	2,400	24	24	48
≥ 60 to < 100	2,700	27	27	54
≥ 100	3,000	30	30	60

[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: Maintenance dose administration reference table for Ultomiris

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	6	6	12
≥ 20 to < 30	2,100	21	21	42
≥ 30 to < 40	2,700	27	27	54
≥ 40 to < 60	3,000	30	30	60
≥ 60 to < 100	3,300	33	33	66
≥ 100	3,600	36	36	72

[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 24: Supplemental dose administration reference table for Ultomiris

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
	1,200	12	12	24
	1,500	15	15	30
≥ 60 to < 100	600	6	6	12
	1,500	15	15	30
	1,800	18	18	36
≥ 100	600	6	6	12
	1,500	15	15	30
	1,800	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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Alexion Pharma International Operations Limited
College Business And Technology Park, Blanchardstown, Dublin 15, Ireland

8. REGISTRATION HOLDER

Alexion Pharma Israel ltd
Pob 7063, Petach Tikva 49170, Israel

9. MARKETING AUTHORISATION NUMBER(S)

Ultomiris 100 mg/mL 37321

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