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

AUSTRALIAN PRODUCT INFORMATION – ULTOMIRIS® (RAVULIZUMAB RCH) 100 MG/ML SOLUTION FOR INTRAVENOUS INFUSION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with Ultomiris. Meningococcal infection may become rapidly life-threatening or fatal if not recognised and treated early (see *section 4.4 Special Warnings and Precautions for Use*).

- **Refer to the most current edition of the Australian Immunisation Handbook for meningococcal vaccination guidelines.**
- **Immunise patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Ultomiris, unless the risks of delaying Ultomiris therapy outweigh the risk of developing a meningococcal infection (see *section 4.4 Special Warnings and Precautions for Use* for additional guidance on the management of the risk of meningococcal infection).**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

1 NAME OF THE MEDICINE

Ravulizumab *rch*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

3 PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ultomiris is indicated for the treatment of patients with:

- Paroxysmal Nocturnal Haemoglobinuria (PNH)
- Atypical Haemolytic Uraemic Syndrome (aHUS)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

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

Table 1 Ultomiris Weight-Based Dosing Regimen

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

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

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

Table 2 Ultomiris Weight-Based Dosing Regimen for paediatric patients < 40 kg

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

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

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

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

Administration of PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) may reduce Ultomiris serum levels. There is no experience with administration of supplemental doses of Ultomiris.

Preparation for Administration

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

Aseptic technique must be used.

Prepare Ultomiris as follows:

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

Each vial of Ultomiris is intended for single use only.

Table 3 Loading Dose Administration Reference Table

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

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

Table 4 Maintenance Dose Administration Reference Table

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

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

Administration

Do not administer as an intravenous push or bolus injection.

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

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

Special Populations

Paediatric population:

Ultomiris has not been studied in PNH patients who weigh less than 30 kg. The posology to be used in paediatric patients with PNH who weigh less than 30 kg is identical to the weight-based dosing recommendations provided for paediatric patients with aHUS based on pharmacokinetic/pharmacodynamic (PK/PD) data available in aHUS and PNH patients treated with Ultomiris.

Elderly (> 65 years old): Ultomiris may be administered to patients with PNH and aHUS aged 65 years and over. There is no evidence indicating any special precautions are required for treating an elderly population,although experience with ravulizumab in elderly patients is limited.

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

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

Hepatic impairment: The safety and efficacy of 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.

4.3 CONTRAINDICATIONS

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

Do not initiate Ultomiris therapy in patients with unresolved *Neisseria meningitidis* infection, see *section 4.4. Special Warnings and Precautions for Use; Serious Meningococcal Infectio*n.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Meningococcal Infection

Due to its mechanism of action, the use of Ultomiris increases the patient's susceptibility to meningococcal infection/sepsis *(Neisseria meningitidis)*. Meningococcal infection due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to administering the first dose of 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 to reduce the risk of infection with the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current medical guidelines for vaccination use.

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

Immunisation

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

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

Other Systemic Infections

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

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

Physicians should advise patients about gonorrhoea prevention.

Infusion Reactions

Administration of Ultomiris may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials conducted with PNH and aHUS patients, infusion reactions were common. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). In case of infusion reaction, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur (see *section 4.8 Adverse Effects (Undesirable Effects), Post-marketing Experience*).

Immunogenicity

Treatment with any therapeutic protein may induce an immune response. In adult PNH studies (n = 261), paediatric PNH study (n=13), and aHUS studies (n = 89), only 2 (0.55%) instances of treatment-emergent anti-drug antibodies have been reported with Ultomiris. These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

Monitoring After Ultomiris Discontinuation

Treatment discontinuation for PNH

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

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

Treatment discontinuation for aHUS

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

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

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

(i) At least two of the following laboratory results observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during 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)

(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, re-initiation of ravulizumab treatment should be considered, beginning with the loading dose and maintenance dose (see *Section 4.2 Dose and Method of Administration)*.

Use in the Elderly

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

Paediatric Use

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

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on fertility have been conducted specifically with ravulizumab *rch*.

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

Use in Pregnancy – Category B2

No clinical data on exposed pregnancies are available.

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

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

Use in Lactation

It is unknown whether ravulizumab *rch* 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most common adverse drug reactions are diarrhoea, nausea, vomiting, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials were meningococcal infection and meningococcal sepsis.

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

PNH Clinical Trial Experience

Adult population with PNH

The data described below reflect exposure of 441 adult patients with PNH from the registration Phase 3 studies with a median treatment duration of 6 months for Ultomiris and 6 months for Soliris.

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

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

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

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

Headache	71 (32)	57 (26)
Dizziness	12 (5)	14 (6)

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

Paediatric population with PNH

In paediatric PNH patients (aged 9 to 17 years) included in the paediatric PNH Phase 3 study, the safety profile appeared similar to that observed in adult PNH patients and in paediatric and adult aHUS patients. The most common adverse events were abdominal pain and upper respiratory tract infection (refer to Table 6 below).

Table 6 Adverse Events Reported in 10% or More of Ultomiris-Treated Paediatric PNH Patients in Study ALXN1210-PNH-304

Body System Adverse Event	**Treatment Naïve**	**Soliris Experienced**	**Total**
	n = 5 n (%)	**n = 8 n (%)**	**n = 13 n (%)**
Blood and lymphatic system disorders			
Anaemia	0 (0)	2 (25)	2 (15)
Gastrointestinal disorders			
Abdominal pain	0 (0)	3 (37)	3 (23)
Abdominal pain upper	0 (0)	2 (25)	2 (15)
Constipation	0 (0)	2 (25)	2 (15)
Diarrhoea	0 (0)	2 (25)	2 (15)
Nausea	0 (0)	2 (25)	2 (15)
General disorders and administration site conditions			
Pyrexia	1 (20)	1 (13)	2 (15)
Infections and infestations			
Upper Respiratory tract infection	1 (20)	6 (75)	7 (54)
COVID-19	2 (40)	0 (0)	2 (15)
Musculoskeletal and connective tissue disorders			
Pain in extremity	0 (0)	2 (25)	2 (15)
Nervous system disorders			
Headache	1 (20)	2 (25)	3 (23)

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

aHUS Clinical Trial Experience

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

Table 7, Table 8 and Table 9 describe the adverse events that occurred at a rate of 10% or more among patients treated with Ultomiris in the aHUS studies.

Serious adverse events were reported in 48 (54%) patients with aHUS receiving Ultomiris. The most frequent serious adverse events reported in more than 2 patients (2.2%) treated with Ultomiris were hypertension, pneumonia and abdominal pain. Four patients died during the ALXN1210-aHUS-311 study. The cause of death was sepsis in 2 patients and intracranial haemorrhage in 1 patient. The fourth patient, who was excluded from the trial after a diagnosis of STEC-HUS, died due to pre-treatment cerebral arterial thrombosis.

Table 7 Adverse Events Reported in 10% or More of Ultomiris-Treated Adult Patients with aHUS in Study ALXN1210-aHUS-311

Body System Adverse Event	N=58	
	All Grades*** (n=53) n (%)	≥ Grade 3 (n=14) n (%)
Blood and lymphatic system disorders		
Anaemia	8 (14)	0 (0)
Gastrointestinal disorders		
Diarrhoea	19 (33)	2 (3)
Vomiting	18 (31)	2 (3)
Nausea	15 (26)	1 (2)
Constipation	9 (16)	1 (2)
Abdominal pain	8 (14)	1 (2)
General disorders and administration site conditions		
Pyrexia	12 (21)	1 (2)
Oedema peripheral	10 (17)	0 (0)
Fatigue	9 (16)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	16 (28)	0 (0)
Urinary tract infection	11 (19)	5 (9)
Gastrointestinal infection**	8 (14)	2 (3)
Metabolism and nutrition disorders		
Hypokalemia	6 (10)	1 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	15 (26)	0 (0)
Back pain	7 (12)	1 (2)
Muscle spasms	6 (10)	0 (0)
Pain in extremity	6 (10)	0 (0)
Nervous system disorders		
Headache	22 (38)	1 (2)
Dizziness	6 (10)	0 (0)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (17)	0 (0)
Dyspnoea	11 (19)	1 (2)
Skin and subcutaneous tissue disorders		
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)

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

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

Table 8 Adverse Events Reported in 10% or More of Ultomiris-Treated Paediatric Patients with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Event	N=31	
	All Grades** (n=28) n (%)	≥ Grade 3 (n=6) n (%)
Gastrointestinal disorders		
Vomiting	8 (26)	1 (3)
Diarrhoea	8 (26)	0 (0)
Abdominal pain	7 (23)	0 (0)
Constipation	4 (13)	0 (0)
Nausea	4 (13)	0 (0)
General disorders and administration site conditions		
Pyrexia	10 (32)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	17 (55)	2 (6)
Pneumonia	4 (13)	2 (6)
Injury, poisoning and procedural complications		
Contusion	4 (13)	0 (0)
Musculoskeletal and connective tissue disorders		
Myalgia	4 (13)	0 (0)
Nervous system disorders		
Headache	8 (26)	1 (3)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (19)	0 (0)
Skin and subcutaneous tissue disorders		
Rash	4 (13)	0 (0)
Vascular disorders		
Hypertension	7 (23)	2 (6)

*: Grouped term includes Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Rhinitis, Viral upper respiratory tract infection, Rhinovirus infection, Viral pharyngitis, Rhinorrhoea, and Oropharyngeal pain. **: Graded per CTCAE v5.0.

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

Table 9 Adverse Events Reported in 10% or More of Ultomiris-Treated Patients from Birth to 18 Years of Age with aHUS in Study ALXN1210-aHUS-312

	Age 0 to <2 (n=4)	Age 2 to <6 (n=10)	Age 6 to < 12 (n=7)	Age 12 to < 18 (n=10)	Total (n=31)
System Organ Class Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders					
Diarrhoea	1 (25)	2 (20)	2 (29)	3 (30)	8 (26)
Vomiting	1 (25)	4 (40)	2 (29)	1 (10)	8 (26)
Abdominal pain	0 (0)	2 (20)	3 (43)	2 (20)	7 (23)
Constipation	0 (0)	3 (30)	1 (14)	0 (0)	4 (13)
Nausea	0 (0)	1 (10)	2 (29)	1 (10)	4 (13)
General disorders and administration site conditions					
Pyrexia	1 (25)	4 (40)	3 (43)	2 (20)	10 (32)
Infections and infestations					
Upper respiratory tract infection*	2 (50)	6 (60)	5 (71)	4 (40)	17 (55)
Pneumonia	1 (25)	0 (0)	2 (29)	1 (10)	4 (13)
Injury, poisoning and procedural complications					
Contusion	0 (0)	1 (10)	2 (29)	1 (10)	4 (13)
Musculoskeletal and connective tissue disorders					
Myalgia	1 (25)	0 (0)	2 (29)	1 (10)	4 (13)
Nervous system disorders					
Headache	0 (0)	0 (0)	5 (71)	3 (30)	8 (26)
Respiratory, thoracic and mediastinal disorders					
Cough	0 (0)	3 (30)	2 (29)	1 (10)	6 (19)
Skin and subcutaneous tissue disorders					
Rash	1 (25)	0 (0)	3 (43)	0 (0)	4 (13)
Vascular disorders					
Hypertension	2 (50)	1 (10)	2 (29)	2 (20)	7 (23)

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

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

Description of selected adverse reactions

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

Post-marketing Experience

Infusion reactions

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

Urticaria

Urticaria has been noted as an uncommon adverse event in patients treated with Ultomiris.

Reporting suspected adverse effects

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

4.9 OVERDOSE

No case of overdose has been reported to date.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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

Mechanism of Action

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

This mechanism of action provides the therapeutic rationale for the use of Ultomiris in PNH, in which uncontrolled complement activation is involved. In patients with PNH, complement-mediated intravascular haemolysis is blocked with Ultomiris treatment.

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

Ultomiris dosing has been optimised to achieve therapeutic steady state concentrations following the first dose, resulting in immediate onset of action and complete terminal complement inhibition by the end of infusion; ravulizumab *rch* half-life in serum yields prolonged pharmacologic activity, allowing dosing once every 8 weeks.

Pharmacodynamic Effects

Following Ultomiris treatment in both 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 (Figure 1 and Figure 2). In contrast, serum free C5 concentrations did not consistently remain < 0.5 µg/mL following Soliris treatment (Figure 1 and Figure 2).

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

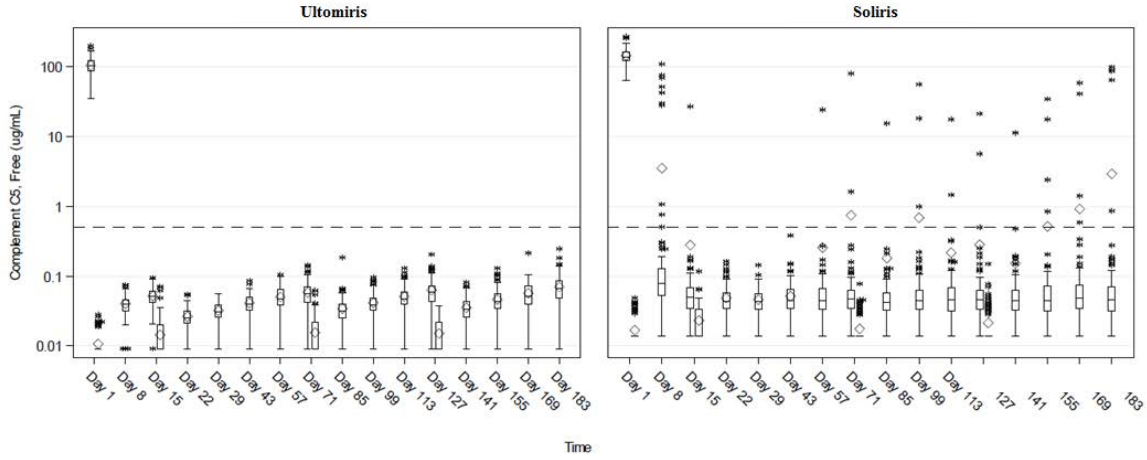
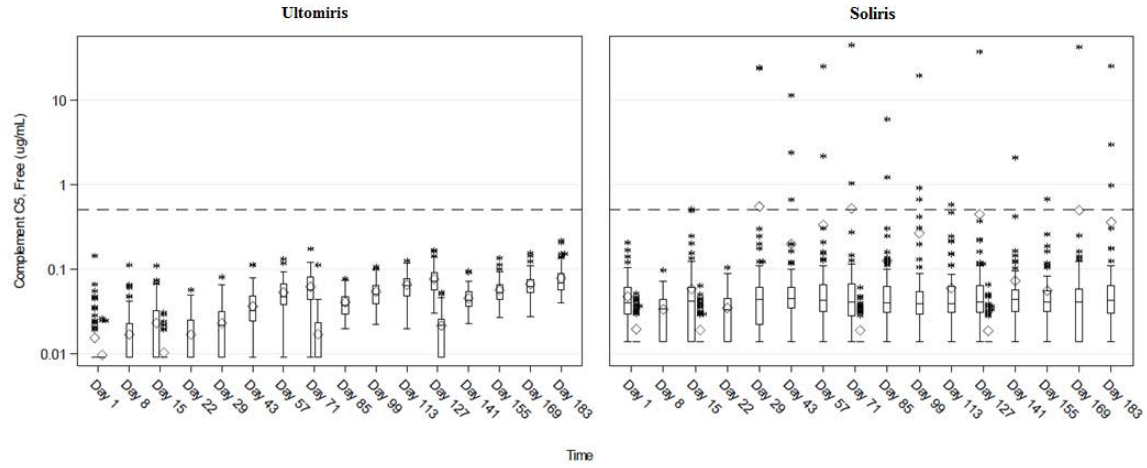


Figure 2: Free C5 vs Time Profiles in Soliris-Experienced Patients with PNH



The extent and duration of the pharmacodynamic response in patients with PNH were exposure dependent for Ultomiris. Free C5 levels of <0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Clinical trials

Paroxysmal Nocturnal Haemoglobinuria (PNH)

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

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

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

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

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

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

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

The Complement-Inhibitor Naïve Study was a 26-week, multicentre, open-label, randomised, active-controlled, Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry.

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

Table 10 presents the baseline characteristics of the PNH patients enrolled in the Complement-Inhibitor Naïve Study.

Table 10 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

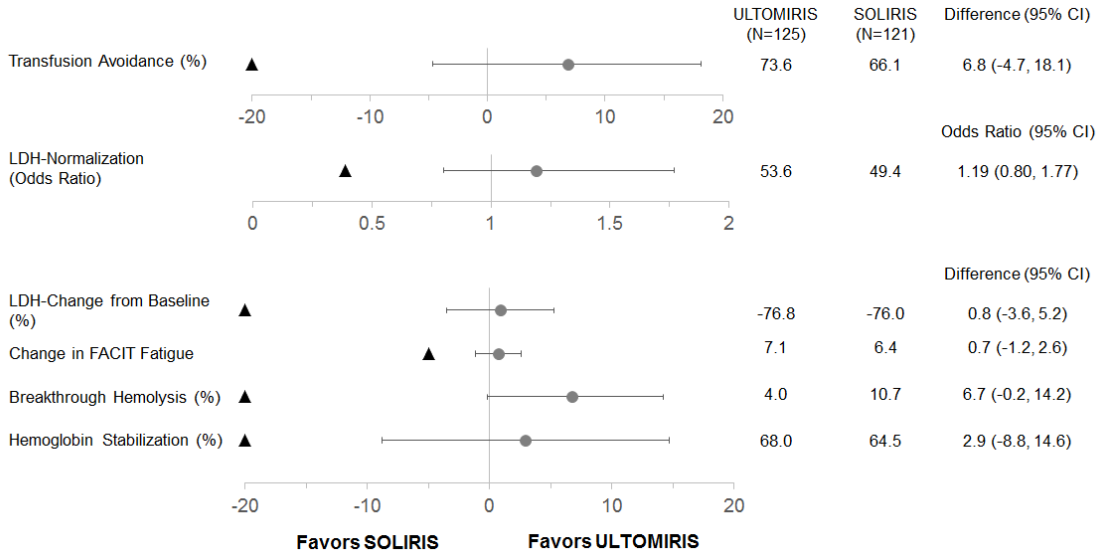
Parameter	Statistics	Ultomiris (n = 125)	Soliris (n = 121)
Age (years) at first infusion in study	Mean (SD) Median Min, max	44.8 (15.16) 43.0 18, 83	46.2 (16.24) 45.0 18, 86
Sex (n, %)	Male Female	65 (52.0) 60 (48.0)	69 (57.0) 52 (43.0)
Pre-treatment LDH levels	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0
Number of patients with packed red blood cells (pRBC)/whole blood transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
pRBC/whole blood transfusions within 12 months prior to first dose	Total Mean (SD) Median	677 6.6 (6.04) 4.0	572 5.7 (5.53) 3.0
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Patients with any PNH conditions prior to informed consent Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[a]	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]"Other" as specified on case report form included thrombocytopenia, chronic kidney disease, and pancytopenia, as well as a number of other conditions.

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

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

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



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

Transfusion avoidance through Day 183 was achieved by 73.6% of patients in the Ultomiris group compared to 66.1% in the Soliris group. The difference between the Ultomiris and Soliris treatment groups in the percentage of patients who avoided transfusion was 6.8% (95% CI: -4.66%, 18.14%). Total number of units transfused was also lower for the Ultomiris group (222 for Soliris vs 155 for Ultomiris). The adjusted prevalence of LDH normalisation (LDH levels ≤ 1 × ULN from Day 29 through Day 183) was 53.6% for the Ultomiris group and 49.4% for the Soliris group. The adjusted odds ratio for LDH normalisation for the comparison of Ultomiris to Soliris was 1.187 (95% CI: 0.796, 1.769). The median time to first LDH normalisation was 24 days for Ultomiris and 29 days for Soliris.

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

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

Breakthrough haemolysis defined as at least one new or worsening symptom or sign of intravascular haemolysis in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy, was experienced by 4.0% of patients in the Ultomiris group and 10.7% of

patients in the Soliris group. The difference between treatment groups was -6.7% (95% CI: -14.21%, 0.18%).

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

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

ALXN1210-PNH-302 Study in adult PNH patients previously treated with Soliris

The Soliris-Experienced Study was a 26-week, multicentre, open-label, randomised, active-controlled Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with Soliris for at least the past 6 months.

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

Table 11 presents the baseline characteristics of the PNH patients enrolled in the Soliris-Experienced Study.

Table 11 Baseline characteristics in the Soliris-Experienced Study

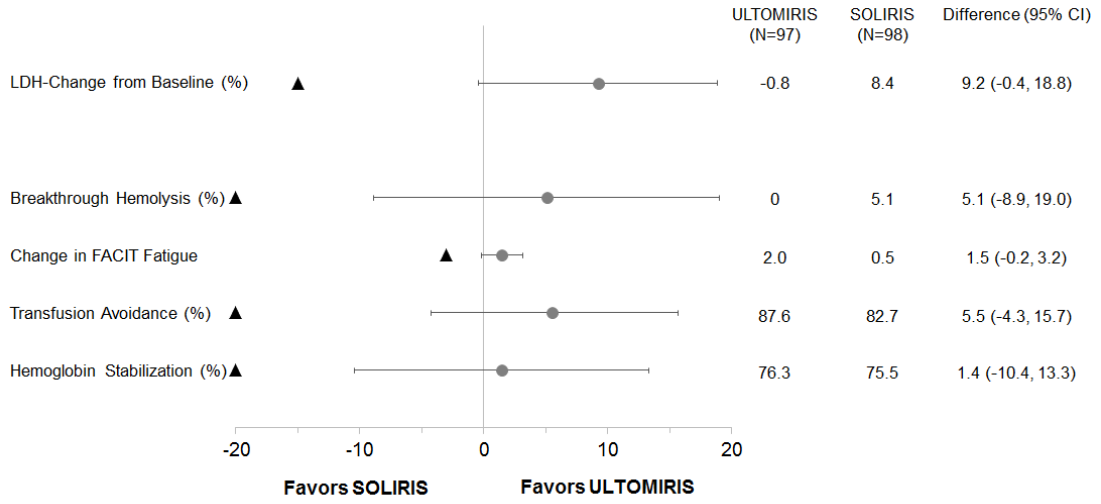
Parameter	Statistics	Ultomiris (n = 97)	Soliris (n = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	50 (51.5) 47 (48.5)	48 (49.0) 50 (51.0)
Pre-treatment LDH levels	Mean (SD) Median	228.0 (48.71) 224.0	235.2 (49.71) 234.0
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose	n (%)	13 (13.4)	12 (12.2)
pRBC/whole blood transfusions within 12 months prior to first dose	Total Mean (SD) Median	64 4.9 (5.51) 3.0	30 2.5 (2.32) 1.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	103 7.9 (8.78) 4.0	50 4.2 (3.83) 2.5
Patients with any PNH conditions prior to informed consent Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[a]	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]"Other" category included neutropenia, renal dysfunction, and thrombocytopenia, as well as a number of other conditions.

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

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

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



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

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

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

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

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

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

As statistically significant non-inferiority was achieved for the primary endpoint and all 4 key secondary endpoints, the pre-specified hierarchical order continued with superiority testing of percent change from baseline in LDH. The assessment of the treatment difference for superiority resulted in a p-value of 0.0583 which did not reach the pre-specified significance threshold for superiority ($p < 0.05$) and therefore no additional testing in the hierarchy was conducted.

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

ALXN1210-PNH-304 Study in paediatric patients with PNH

The paediatric study is a multi-centre, open-label, Phase 3 study conducted in Soliris-experienced and complement inhibitor treatment naïve paediatric patients with PNH. Patients who completed the 26-week primary evaluation period are to be followed for up to 4 years in the long-term Extension Period.

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

Table 12 presents the baseline characteristics of the PNH patients enrolled in the Paediatric PNH Study.

Table 12: Demographics and Baseline Characteristics- Full Analysis Set

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

Variable	Treatment-Naïve (n = 5)	Eculizumab-Experienced (n = 8)
Baseline Weight (kg) Mean (SD) Median (min, max)	 56.26 (11.594) 55.60 (39.5, 72.0)	 56.25 (12.247) 55.50 (36.7, 69.0)
Baseline weight (kg), n (%) ≥ 30 to < 40 kg ≥ 40 to < 60 kg ≥ 60 to < 100 kg	 1 (20.0) 3 (60.0) 1 (20.0)	 1 (12.5) 4 (50.0) 3 (37.5)
Pre-treatment LDH levels (U/L) Median (min, max)	 588.50 (444, 2269.7)	 251.50 (140.5, 487)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	2 (40.0)	2 (25.0)
Number of pRBC/whole blood transfusions within 12 months prior to first dose Total 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 (%) Anemia Hematuria or hemoglobinuria Aplastic anemia 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)

[a] Other PNH-associated conditions were reported as “renal and splenic infarcts” and “multiple lesions concerning for embolic process”.
Note: Percentages were based on the total number of patients in each cohort, or overall.
Abbreviations: max = maximum; min = minimum; SD = standard deviation

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

Table 13 presents secondary efficacy outcomes for the Primary Evaluation Period.

Table 13 Secondary efficacy outcomes from the interim analysis of Paediatric study in PNH patients - 26-week Primary Evaluation Period

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

Abbreviations: LDH = lactate dehydrogenase

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

atypical Haemolytic Uraemic Syndrome (aHUS)

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

ALXN1210-aHUS-311 Study in adult patients with aHUS

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

A total of 58 patients with documented aHUS were enrolled. Enrolment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related haemolytic uraemic 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. The majority of patients (92.9%) had extra renal signs or symptoms of aHUS at baseline. At baseline, 71.4% (n = 41) of patients had Stage 5 chronic kidney disease (CKD).

Table 14 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 14 Baseline Characteristics in the Adult aHUS Study

Parameter	Statistics	Ultomiris (n = 56)
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male Female	n (%)	 19 (33.9) 37 (66.1)
Race [a] Asian White Unknown Other	n (%)	 15 (26.8) 29 (51.8) 8 (14.3) 4 (7.2)
Any pre-treatment extra-renal signs or symptoms of aHUS Cardiovascular Pulmonary Central nervous system Gastrointestinal Skin Skeletal muscle	n (%)	52 (92.9) 39 (69.6) 25 (44.6) 29 (51.8) 35 (62.5) 17 (30.4) 13 (23.2)
History of transplant	n (%)	8 (14.3)
Patients post partum	n (%)	8 (14.3)
Platelets (10^9/L) blood [normal range 130 to 400 × 10^9/L]	n Mean (SD) Median (min,max)	56 118.52 (86.440) 95.25 (18, 473)
Haemoglobin (g/L) blood [normal range 115 to 160 g/L (female), 130 to 175 g/L (male)]	n Mean (SD) Median (min,max)	56 86.26 (14.866) 85.00 (60.5, 140)
LDH (U/L) serum [normal range 120 to 246 U/L]	n Mean (SD) Median (min,max)	56 702.38 (557.959) 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	n (%) Mean (SD) Median (min,max)	55 15.86 (14.815) 10.00 (4, 80)
Patients on dialysis	n (%)	29 (51.8)

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

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

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week Initial Evaluation Period as shown in Table 15.

Table 15 Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period

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

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

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 normalisation, 47 (83.9%; 95% CI: 73.4%, 94.4%) patients for LDH normalisation, 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 and occurred as early as 7 days following the first dose of Ultomiris. The latest response was observed at 401 days. An increase in mean platelet count was observed rapidly after commencement of Ultomiris, 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). Table 16 summarises the secondary efficacy results for Study ALXN1210-aHUS-311.

Renal function, as measured by eGFR, was improved or maintained during Ultomiris treatment. Two thirds of the patient population (32/47), who were mostly CKD Stage 4 or 5 at baseline, improved by 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. Seventeen 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 16 Secondary Efficacy Outcomes for Study in Adult Patients with aHUS

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

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

ALXN1210-aHUS-312 Study in paediatric patients with aHUS

Study ALXN1210-aHUS-312 is a 26-week ongoing, multicentre, single arm, Phase 3 study conducted in paediatric 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. The median age at the time of first infusion was 5.2 years (range: 0.9, 17.3 years). Enrolment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related haemolytic uraemic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism.

The overall mean weight at baseline was 22.2 kg; the majority of patients (50%) were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (72.2%) had pre-treatment 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 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 Ultomiris in patients refractory to Soliris.

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

Table 17 Demographics and Baseline Characteristics in Paediatric Study in Patients with aHUS

Parameter	Statistics	Ultomiris (Naïve, n = 18)	Ultomiris (Switch, n = 10)
Age at time of first infusion (years) category			
Birth to < 2 years	n (%)	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			
Male	n (%)	8 (44.4)	9 (90.0)
Female		10 (55.6)	1 (10.0)
Race[a]			
Asian	n (%)	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)
Other		1 (5.6)	0 (0.0)
Any pre-treatment extra-renal signs or symptoms of aHUS		13 (72.2)	1 (10.0)
Cardiovascular		9 (50.0)	1 (10.0)
Pulmonary		1 (5.6)	0 (0)
Central Nervous System	n (%)	7 (38.9)	0 (0)
Gastrointestinal		11 (61.1)	0 (0)
Skin		9 (50.0)	0 (0)
Skeletal muscle		1 (5.6)	0 (0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelets (10^9/L) blood [normal range 229 to 533 × 10^9/L]	Mean (SD) Median (min, max)	60.4 (32.61) 51.3 (14, 125)	287.9 (74.59) 281.8 (207, 415.5)
Haemoglobin (g/L) blood [normal range 107 to 131 g/L]	Mean (SD) Median (min, max)	74.4 (17.38) 74.3 (32, 106)	131.5 (11.31) 132.0 (114.5, 148)

LDH (U/L) serum [normal range 165 to 395 U/L]	Mean (SD) Median (min, max)	2223.5 (1321.12) 1963.0 (772, 4985)	219.4 (56.85) 206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	Mean (SD) Median (min, max)	26.4 (21.17) 22.0 (10, 84)	104.9 (29.55) 99.8 (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 haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. 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

	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 normalisation	18	17	0.944 (0.727, 0.999)
LDH normalisation	18	16	0.889 (0.653, 0.986)
≥25% improvement in serum creatinine from baseline	18	15	0.833 (0.586, 0.964)
Haematologic normalisation	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 (range: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 Ultomiris, 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%) paediatric 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 each for platelet count normalisation, LDH normalisation, and renal function improvement.

Table 19 summarises the secondary efficacy results for Study ALXN1210-aHUS-312. 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 Secondary Efficacy Outcomes for Paediatric Study in Patients with aHUS

Parameters	n=18	
Haematologic TMA parameters, Day 183	Observed value (n=17)	Change from baseline (n=17)
Platelets (10^9/L) blood		
Mean (SD)	304.94 (75.711)	245.59 (91.827)
Median	318.00	247.00
LDH (U/L) serum		
Mean (SD)	262.41 (59.995)	-2044.13 (1328.059)
Median	247.00	-1851.50
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/N	16/18	
proportion (95% CI)*	0.889 (0.653, 0.986)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	15/17	
Proportion (95% CI)*	0.882 (0.636, 0.985)	
Worsened[b]		
m/n	0/11	
Proportion (95% CI)*	0.000 (0.000, 0.285)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=17)	Change from baseline (n=17)
Mean (SD)	108.5 (56.87)	85.4 (54.33)
Median	108.0	80.00

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

The efficacy of Ultomiris for the treatment of aHUS appear similar in paediatric and adult patients.

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

5.2 PHARMACOKINETIC PROPERTIES

A linear, 2-compartment PK model was developed that adequately described the observed ravulizumab *rch* PK following IV administration. The estimated mean (SD) clearance, central volume and terminal elimination half-life following multiple dosing of ravulizumab *rch* in all Phase 3 patients with PNH were 3.32 (0.94) mL/hr, 3.45 (0.65) L, and 49.7 (8.9) days, respectively. Steady state therapeutic concentrations are achieved immediately following the first dose of Ultomiris. In PNH patients, pharmacodynamic activity correlates directly with ravulizumab *rch* serum concentrations above the target exposure level results in free C5 levels < 0.5 µg/mL, achieving immediate, complete and sustained blockade of haemolytic activity in all PNH patients.

Absorption

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

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state for patients with PNH on the studied weight-based dose regimen was 5.35 (0.92) L.

Metabolism and Excretion

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab *rch* is expected to be metabolised in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab *rch* contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab *rch* in patients with PNH are 49.7 (8.9) days and 0.00332 (0.000941) L/h, respectively.

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

Special Populations

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

monobasic sodium phosphate
dibasic sodium phosphate
polysorbate 80
L-arginine
Sucrose
Water for injections

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

6.2 INCOMPATIBILITIES

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

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

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

Vials must not be frozen or shaken.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass vial with a stopper and a seal.

Pack size of one vial.

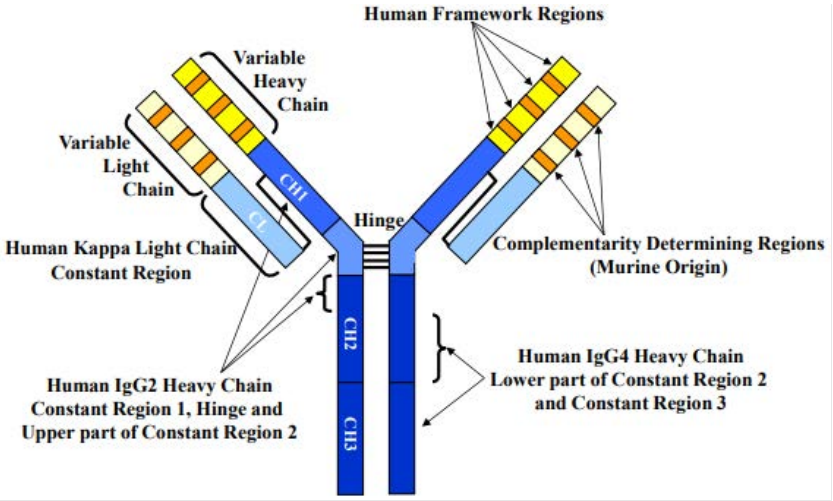
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

CAS registry number: 1803171-55-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 MAR 2021

10 DATE OF REVISION

16 AUG 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Updated details relating to extension of indication application to add paediatric Paroxysmal Nocturnal Haemoglobinuria and Atypical Haemolytic Uraemic Syndrome