SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris

Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 30 mL contains 300 mg of ravulizumab, produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

After dilution, the final concentration of the solution to be infused is 5 mg/mL.

Excipient(s) with known effect:
Sodium (5 mmol per vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear to translucent, slight whitish colour, pH 7.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (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 (see section 5.1).

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

Posology

Adult patients with PNH and aHUS
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 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: Ravulizumab weight-based dosing regimen

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

*Maintenance dose is administered 2 weeks after loading dose

Ravulizumab has not been studied in patients with PNH who weigh less than 40 kg.

There is no experience of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) use with ravulizumab. Administration of PE/PI may reduce ravulizumab serum levels.

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 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).

Special populations

Elderly population (> 65 years old)
No dose adjustment is required for patients with PNH and aHUS 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 is limited.

Renal impairment
In aHUS clinical trials, patients with renal impairment including on dialysis were included. No dose adjustment is required in this population, 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 aHUS with body weight ≥ 40 kg are treated in accordance with the adult dosing recommendations. The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg is shown in Table 2.

Table 2: Ravulizumab weight-based dosing regimen for paediatric patient 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

*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.

The safety and efficacy of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available.

Method of administration

For intravenous infusion only.
Ultomiris must be diluted to a final concentration of 5 mg/mL.
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 must be diluted prior to administration by intravenous infusion over a minimal period of 1.7 to 2.4 hours depending of body weight, see Table 3 below.

Table 3: Dose administration rate

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	113 (1.9)	600	113 (1.9)
≥ 20 to < 30	900	86 (1.5)	2,100	194 (3.3)
≥ 30 to < 40	1,200	77 (1.3)	2,700	167 (2.8)
≥ 40 to < 60	2,400	114 (1.9)	3,000	140 (2.4)
≥ 60 to < 100	2,700	102 (1.7)	3,300	120 (2.0)
≥ 100	3,000	108 (1.8)	3,600	132 (2.2)

[a] Body weight at time of treatment.

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. 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 serogroups A, C, Y, W135 and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use. 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 meningococcal infections/sepsis have been reported in patients treated with ravulizumab. Cases of serious or fatal meningococcal infections/sepsis have been reported 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 information brochure and a patient safety card.

Immunization

Prior to initiating ravulizumab therapy, it is recommended that PNH and aHUS patients initiate immunizations according to current immunization guidelines.

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 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 Leaflet to increase their awareness of potential serious infections and their signs and symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion reactions

Administration of ravulizumab may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials with PNH and aHUS, [(6 out of 487 patients with PNH) and (4 of 89 patients with aHUS)] patients experienced infusion reactions which were mild in severity and transient [e.g., 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.

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:
(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)
Or
(ii) any one of the following symptoms of TMA: a change in mental status or seizures or other extra-renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea; or thrombosis.
If TMA complications occur after ravulizumab discontinuation, consider reinitiation of ravulizumab treatment beginning with the loading dose and maintenance dose described in section 4.2.

Sodium content

This medicinal product when diluted with sodium chloride 9 mg/mL (0.9 %) solution for injection contains 2.65 g sodium per 720 mL at the maximal dose, equivalent to 133 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception methods during treatment and up to 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 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 up to 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 drug reactions (very common frequency) are diarrhoea, nausea, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infection and meningococcal sepsis (see section 4.4).

Tabulated list of adverse reactions

Table 4 gives the adverse reactions observed from PNH and aHUS 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 frequency.

Table 4: Adverse reactions

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

[a] Meningococcal infection includes preferred terms of meningococcal infection and meningococcal sepsis

[b] Estimated from post-marketing experience

Description of selected adverse reactions

Meningococcal infection/sepsis
Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ravulizumab; all 3 had been vaccinated. All 3 recovered while continuing treatment with ravulizumab. In aHUS studies, no meningococcal infections occurred among 89 patients receiving treatment with ravulizumab. Please refer to section 4.4 for information on prevention and treatment of suspected meningococcal infection. Meningococcal infections in patients treated with ravulizumab presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek medical care immediately.

Immunogenicity
Treatment with any therapeutic protein may induce an immune response. In PNH patient studies (N = 261) and aHUS studies (N=89), only 2 (0.57 %) cases of development of

treatment-emergent anti-drug antibody have been reported with ravulizumab. These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

Paediatric population
In paediatric patients with evidence of aHUS (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 reaction reported in paediatric patients was pyrexia.

The safety of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available.

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

No case of overdose has been reported to date.
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA43

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 terminal complement complex [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 complement-inhibitor naïve patients and eculizumab-experienced patients with PNH in Phase 3 studies, immediate and complete inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all patients. Immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS by the end of the first infusion and throughout the 26-week treatment period.

The extent and duration of the pharmacodynamic response in patients with PNH and aHUS 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.

Clinical efficacy and safety

Paroxysmal Nocturnal Haemoglobinuria
The safety and efficacy of ravulizumab in 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 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 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. 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 5 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 5: 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	n (%)	121 (96.8)	120 (99.2)
Anaemia		103 (82.4)	105 (86.8)
Haematuria or haemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anaemia		41 (32.8)	38 (31.4)
Renal failure		19 (15.2)	11 (9.1)
Myelodysplastic syndrome		7 (5.6)	6 (5.0)
Pregnancy complication		3 (2.4)	4 (3.3)
Other[b]		27 (21.6)	13 (10.7)

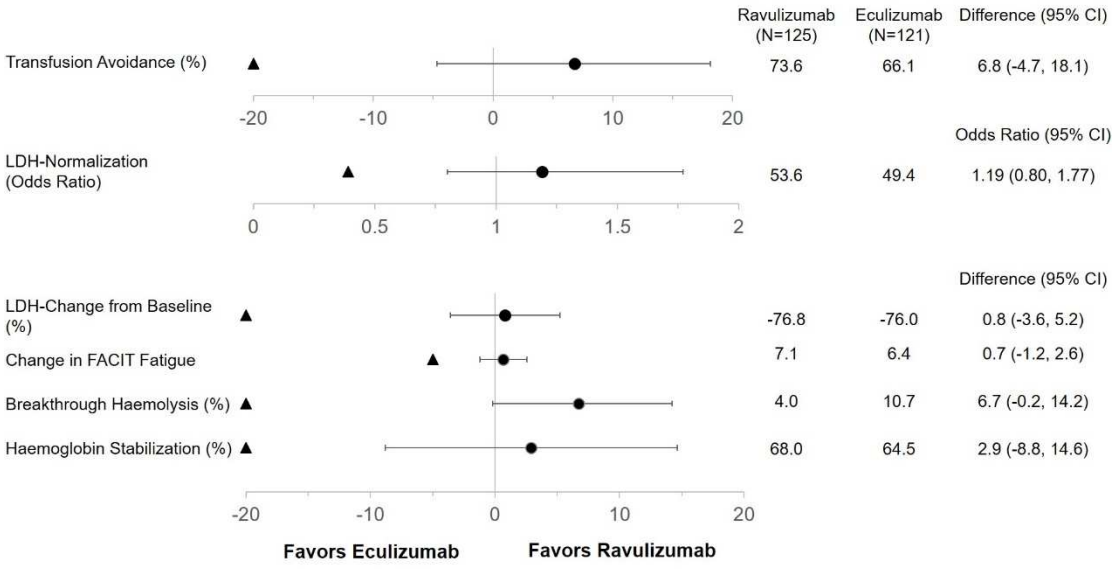
[a] Based on medical history.

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

The coprimary endpoints were transfusion avoidance, and 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 stabilized 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.

Study in PNH patients previously treated with eculizumab

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.

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 6 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 6: Baseline characteristics in the eculizumab-experienced study

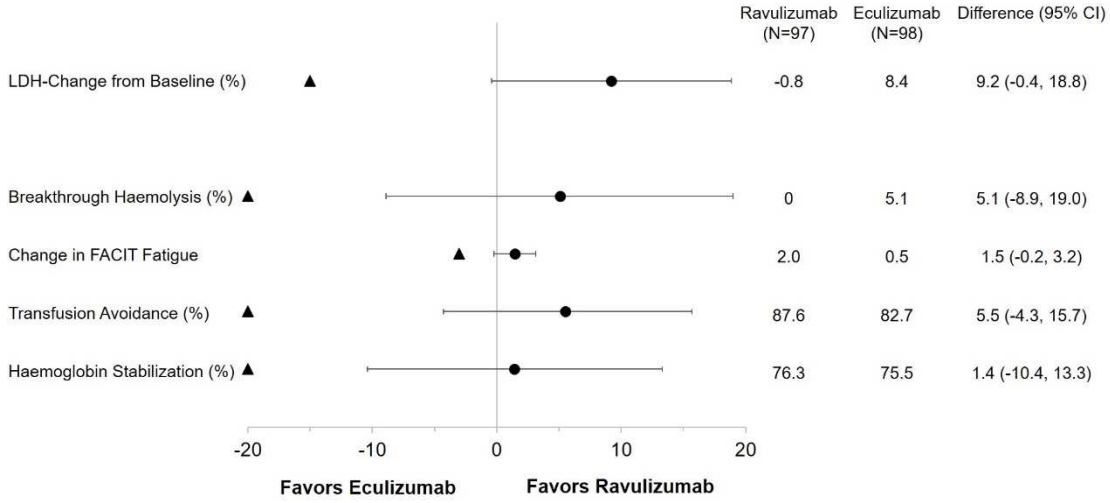
Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	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[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] 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.

Atypical Haemolytic Uremic Syndrome (aHUS)

Study in adult patients with aHUS

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 thrombotic thrombocytopenic purpura (TTP) or Shiga toxin *Escherichia coli* related haemolytic uremic syndrome (STEC HUS). Two patients were excluded from the Full Analysis Set due to a confirmed diagnosis of STEC HUS. Ninety-three percent of patients had extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline.

Table 7 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 7: Baseline characteristics in the adult study

Parameter	**Statistics**	**Ravulizumab (N = 56)**
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male	 n (%)	 19 (33.9)
Race [a] Asian White Other	n (%)	 15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelets (10^9/L) blood	n Median (min,max)	56 95.25 (18, 473)
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: aHUS = atypical haemolytic uremic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by 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 8.

Table 8: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (ALXN1210 aHUS 311)

	Total	**Responder**	
		n	**Proportion (95% CI)[a]**
Complete TMA Response	56	30	0.536 (0.396, 0.675)
Components of Complete TMA Response			
Platelet count 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 normalization, 47 (83.9%; 95% CI: 73.4%, 94.4%) patients for LDH normalization, and 35 (62.5%; 95% CI: 48.9%, 76.1%) patients for renal function improvement.

Complete TMA Response was achieved at a median time of 86 days (7 to 169 days). An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 118.52 × 10^9/L at baseline to 240.34 × 10^9/L at Day 8 and remaining above 227 × 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).

Of the patients who presented at CKD Stage 5, 67.6% (23/34) showed an improvement of 1 or more CKD Stages. Chronic kidney disease stage continued to improve for many patients

(19/30) after achieving Complete TMA Response during the 26-week Initial Evaluation Period.-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 9 summarises the secondary efficacy outcomes for Study ALXN1210-aHUS-311.

Table 9: Secondary Efficacy Outcome for 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	237.96 (73.528)	
Mean (SD)	232.00	114.79 (105.568)
Median		125.00
LDH (U/L) serum	194.46 (58.099)	
Mean (SD)	176.50	-519.83 (572.467)
Median		-310.75
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period	40/56	
m/n	0.714 (0.587, 0.842)	
proportion (95% CI)**		
CKD stage shift from baseline, Day 183		
Improved[a]	32/47	
m/n	0.681 (0.529, 0.809)	
Proportion (95% CI)*		
Worsened[b]	2/13	
m/n	0.154 (0.019, 0.454)	
Proportion (95% CI)*		
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; Therapy; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Paediatric population

Paroxysmal Nocturnal Haemoglobinuria

Ultomiris has not been evaluated in paediatric patients with PNH.

The European Medicines Agency has deferred the obligation to submit the results of studies with Ultomiris in one or more subsets of the paediatric population in paroxysmal nocturnal haemoglobinuria (see section 4.2 for information on paediatric use).

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

The Paediatric Study is a 26-week ongoing, multicenter, single arm, Phase 3 study conducted in paediatric patients.
A total of 21 eculizumab-naïve patients with documented diagnosis of aHUS and evidence of TMA were enrolled, of which 18 were included in the Full Analysis set. Enrolment criteria excluded patients presenting with TMA due to TTP and STEC-HUS. Two patients were given a single dose, and one patient received 2 doses, but then discontinued and were excluded from the Full Analysis Set because aHUS was not confirmed. The overall mean weight at baseline was 22.2 kg;majority of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (72.2%) had pretreatment extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 33.3% (n = 6) of patients had CKD Stage 5.

A total of 10 patients, who switched from 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/1.73m2). Consequently, there is no information on the use of ravulizumab in patient refractory to eculizumab.

Table 10 presents the baseline characteristics of the paediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 10: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-312

Parameter	**Statistics**	**Ravulizumab (Naïve, N = 18)**	**Ravulizumab (Switch, N = 10)**
Age at time of first infusion (years) category	n (%)		
Birth to < 2 years		2 (11.1)	1 (10.0)
2 to < 6 years		9 (50.0)	1 (10.0)
6 to < 12 years		5 (27.8)	1 (10.0)
12 to < 18 years		2 (11.1)	7 (70.0)
Sex	n (%)		
Male		8 (44.4)	9 (90.0)
Race[a]	n (%)		
American Indian or Alaskan Native		1 (5.6)	0 (0.0)
Asian		5 (27.8)	4 (40.0)
Black or African American		3 (16.7)	1 (10.0)
White		9 (50.0)	5 (50.0)
Unknown		1 (5.6)	0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelets (10^9/L) blood	Median (min, max)	51.25 (14, 125)	281.75 (207, 415.5)
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 (%)	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 uremic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet ≥ 150 x 10^9/L and LDH ≤246 U/L) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 14 of the 18 naïve patients (77.8%) during the 26-week Initial Evaluation Period as shown in Table 11.

Table 11: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (ALXN1210-aHUS-312)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	18	14	0.778 (0.524, 0.936)
Components of Complete TMA Response			
Platelet count 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 (15 to 97 days). All patients with Complete TMA Response maintained it through the Initial Evaluation Period with continuous improvements seen in renal function. An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 60.50 × 109/L at baseline to 296.67 × 109/L at Day 8 and remained above 296 × 109/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 for platelet count normalization, 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for LDH normalization, and 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for renal function improvement.

All 6 of the 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 12 summarises the secondary efficacy results for Study ALXN1210-aHUS-312.

Table 12: Secondary Efficacy Outcome for Study ALXN1210-aHUS-312

Parameters	Study ALXN1210-aHUS-312 (N=18)	
Haematologic TMA parameters, Day 183	Observed value (n=17)	Change from baseline (n=17)
Platelets (10^9/L) blood	304.94 (75.711)	
Mean (SD)	318.00	245.59 (91.827)
Median		247.00
LDH (U/L) serum	262.41 (59.995)	
Mean (SD)	247.00	-2044.13 (1328.059)
Median		-1851.50
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period	16/18	
m/N	0.889 (0.653, 0.986)	
proportion (95% CI)*		
CKD stage shift from baseline, Day 183		
Improved[a]	15/17	
m/n	0.882 (0.636, 0.985)	
Proportion (95% CI)*		
Worsened[b]	0/11	
m/n	0.000 (0.000, 0.285)	
Proportion (95% CI)*		
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.

5.2 Pharmacokinetic properties

Absorption

Because the route of ravulizumab administration is an intravenous 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 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]) volume of distribution at steady state for patients with PNH and aHUS on the studied weight-based dose regimen was 5.35 (0.92) L and 5.22 (1.85) L respectively.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with PNH and aHUS are 49.7 (8.9) days and 0.08 (0.022) L/day and 51.8 (16.2) days and 0.08 (0.04) L/day, respectively.

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 and aHUS, resulting in lower exposures in heavier patients. Weight-based dosing is proposed in section 4.2, Table 1.

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 or aHUS, 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

Sodium chloride
Dibasic sodium phosphate
Monobasic sodium phosphate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
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 with sodium chloride 9 mg/ml (0.9%) solution, 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 6 hours at room temperature.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C)
Do not freeze.
Protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only.

Ultomiris requires dilution to a final concentration of 5 mg/mL.

Aseptic technique must be used.

Prepare Ultomiris as follows:
1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section 4.2.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9 %) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 5 mg/mL.

5. The prepared solution should be administered immediately following preparation unless it is stored at 2-8°C. If stored at 2-8°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 13 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 6 hours at room temperature taking into account the expected infusion time.

Table 13: Loading dose administration reference table

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	900	90	90	180
≥ 30 to < 40	1200	120	120	240
≥ 40 to < 60	2,400	240	240	480
≥ 60 to < 100	2,700	270	270	540
≥ 100	3,000	300	300	600

[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 14: Maintenance dose administration reference table

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	2100	210	210	420
≥ 30 to < 40	2700	270	270	540
≥ 40 to < 60	3,000	300	300	600
≥ 60 to < 100	3,300	330	330	660
≥ 100	3,600	360	360	720

[a] Body weight at time of treatment.
[b] Ultomiris should only be 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

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8. REGISTRATION HOLDER

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9. MARKETING AUTHORISATION NUMBER(S)

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