ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/3 mL concentrate for solution for infusion
Ultomiris 1 100 mg/11 mL concentrate for solution for infusion
Ultomiris 300 mg/30 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Ultomiris 300 mg/3 mL concentrate for solution for infusion

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

Excipient(s) with known effect:
Sodium (4.6 mg per 3 mL vial)

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

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

Excipient(s) with known effect:
Sodium (16.8 mg per 11 mL vial)

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Each vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL).
After dilution, the final concentration of the solution to be infused is 5 mg/mL.

Excipient(s) with known effect:
Sodium (115 mg per 30 mL vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

Translucent, clear to yellowish colour, pH 7.4 solution.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Clear to translucent, slight whitish colour, pH 7.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paroxysmal nocturnal haemoglobinuria (PNH)

Ultomiris is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with PNH:
- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Atypical haemolytic uremic syndrome (aHUS)

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

Generalised myasthenia gravis (gMG)

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

Neuromyelitis optica spectrum disorder (NMOSD)

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

4.2 Posology and method of administration

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

Posology

Adult patients with PNH, aHUS, gMG, or NMOSD
The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

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

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

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

* First maintenance dose is administered 2 weeks after loading dose

Treatment initiation instructions in patients who are complement-inhibitor treatment-naïve or switching treatment from eculizumab or ravulizumab solution for injection subcutaneous formulation are shown in Table 2.

Table 2: Ravulizumab treatment initiation instructions

Population	**Weight-based ravulizumab intravenous loading dose**	**Time of first ravulizumab intravenous weight-based maintenance dose**
Not currently on ravulizumab or eculizumab treatment	At treatment start	2 weeks after ravulizumab intravenous loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after ravulizumab intravenous loading dose
Currently treated with ravulizumab subcutaneous formulation*	Not applicable	1 week after last ravulizumab subcutaneous maintenance dose

*Adult patients with PNH or aHUS only

Paediatric patients with PNH or aHUS

Paediatric patients with body weight ≥ 40 kg

These patients should be treated in accordance with the adult dosing recommendations (See Table 1).

Paediatric patients with body weight ⩾ 10 kg to < 40 kg

The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg are shown in Table 3.
For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses should be administered per weight-based dosing regimen shown in Table 3, starting 2 weeks after loading dose administration.

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

Body weight range (kg)	**Loading dose (mg)**	**Maintenance dose (mg)***	**Dosing interval**
⩾ 10 to < 20	600	600	Every 4 weeks
⩾ 20 to < 30	900	2,100	Every 8 weeks
⩾ 30 to < 40	1,200	2,700	Every 8 weeks

* First maintenance dose is administered 2 weeks after loading dose

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

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

In aHUS, ravulizumab treatment to resolve thrombotic microangiopathy (TMA) manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy (see section 4.4).

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

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

Supplemental dosing following treatment with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg)
Plasma exchange (PE), plasmapheresis (PP) and intravenous immunoglobulin (IVIg) have been shown to reduce ravulizumab serum levels. A supplemental dose of ravulizumab is required in the setting of PE, PP or IVIg (Table 4).

Table 4: Supplemental dose of ravulizumab after PP, PE, or IVIg

Body weight range (kg)	**Most recent ravulizumab dose (mg)**	**Supplemental dose (mg) following each PE or PP intervention**	**Supplemental dose (mg) following completion of an IVIg cycle**
≥ 40 to < 60	2,400	1,200	600
	3,000	1,500	
≥ 60 to < 100	2,700	1,500	600
	3,300	1,800	
≥ 100	3,000	1,500	600
	3,600	1,800	
Timing of ravulizumab supplemental dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

Abbreviations: IVIg = intravenous immunoglobulin, kg = kilogram, PE = plasma exchange, PP = plasmapheresis

Treatment switch from ravulizumab intravenous formulation to ravulizumab subcutaneous formulation
In the maintenance phase, adult patients with PNH or aHUS treated with ravulizumab intravenous formulation have the possibility to switch to ravulizumab subcutaneous formulation in agreement with their treating physician. For posology recommendations about the subcutaneous maintenance dose, see section 4.2 of Ultomiris solution for injection in cartridge summary of product characteristics (SmPC).

Treatment initiation instructions of ravulizumab subcutaneous formulation in patients treated with ravulizumab intravenous formulation are shown in Table 5.

Table 5: Ravulizumab subcutaneous formulation treatment initiation instructions (adult patients with PNH or aHUS)

Population	**Weight-based ravulizumab intravenous loading dose**	**Time of first ravulizumab 490mg subcutaneous maintenance dose**
Currently treated with ravulizumab intravenous formulation	Not applicable	8 weeks after last ravulizumab intravenous maintenance dose

Special populations

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

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

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

Paediatric population

The safety and efficacy or ravulizumab in children with a body weight below 10 kg with PNH or aHUS have not been established. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

The safety and efficacy or ravulizumab in children with gMG or NMOSD have not been established. No data are available.

Method of administration

For intravenous infusion only. The concentrate for solution for infusion is not intended for subcutaneous administration.
This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.

Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1 100 mg/11 mL concentrates for solution for infusion.

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

Ultomiris concentrate for solution for infusion is presented as 3 mL and 11 mL vials (100 mg/mL) and must be diluted to a final concentration of 50 mg/mL. Following dilution, Ultomiris is to be administered by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 0.17 to 1.3 hours (10 to 75 minutes) depending on body weight (see Table 6 and Table 7 below).

Table 6: Dose administration rate for Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

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

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

Table 7: Dose administration rate for supplemental doses of Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

Body weight range (kg)[a]	Supplemental dose[b] (mg)	Minimum infusion duration minutes (hours)
≥ 40 to < 60	600	15 (0.25)
	1,200	25 (0.42)
	1,500	30 (0.5)
≥ 60 to < 100	600	12 (0.20)
	1,500	22 (0.36)
	1,800	25 (0.42)
≥ 100	600	10 (0.17)
	1,500	15 (0.25)
	1,800	17 (0.28)

[a] Body weight at time of treatment.
[b] Refer to Table 4 for selection of ravulizumab supplemental dose

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Ultomiris concentrate for solution for infusion is presented as 30 mL vial (10 mg/mL) and must be diluted to a final concentration of 5 mg/mL. Following dilution, Ultomiris is to be administered by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 0.4 to 3.3 hours (22 to 194 minutes) depending on body weight (see Table 8 and Table 9 below).

Table 8: Dose administration rate for Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
⩾ 10 to < 20[b]	600	113 (1.9)	600	113 (1.9)
⩾ 20 to < 30[b]	900	86 (1.5)	2,100	194 (3.3)
⩾ 30 to < 40[b]	1,200	77 (1.3)	2,700	167 (2.8)
⩾ 40 to < 60	2,400	114 (1.9)	3,000	140 (2.3)
⩾ 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.
[b] For PNH and aHUS indications only

Table 9: Dose administration rate for supplemental doses of Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight range (kg)[a]	Supplemental dose [b] (mg)	Minimum infusion duration minutes (hours)
≥ 40 to < 60	600	30 (0.5)
	1,200	60 (1.0)
	1,500	72 (1.2)
≥ 60 to < 100	600	23 (0.4)
	1,500	60 (1.0)
	1,800	65 (1.1)
≥ 100	600	22 (0.4)
	1,500	60 (1.0)
	1,800	65 (1.1)

[a] Body weight at time of treatment.
[b] Refer to Table 4 for selection of ravulizumab supplemental dose

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

Traceability

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

Serious meningococcal infection

Due to its mechanism of action, the use of ravulizumab increases the patient's susceptibility to meningococcal infection/sepsis (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur (see section 4.8). To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to initiating ravulizumab unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. Patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against 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 or fatal meningococcal infections/sepsis have been reported in patients treated with ravulizumab and in patients treated with other terminal complement inhibitors. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. Physicians should provide patients with a patient information brochure and a Patient card.

Immunisation

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

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

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

Other systemic infections

Ravulizumab therapy should be administered with caution to patients with active systemic infections. Ravulizumab blocks terminal complement activation; therefore, patients may have increased susceptibility to infections caused by *Neisseria* species and encapsulated bacteria. Serious infections

with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.
Patients should be provided with information from the Package Information Leaflet to increase their awareness of potential serious infections and their signs and symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion-related reactions

Administration of ravulizumab may result in systemic infusion-related reactions and allergic or hypersensitivity reactions, including anaphylaxis (see section 4.8).

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

Treatment discontinuation for PNH

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

Treatment discontinuation for aHUS

There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.
If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe TMA complications.
TMA complications post-discontinuation can be identified if any of the following is observed:

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

If TMA complications occur after ravulizumab discontinuation, reinitiation of ravulizumab treatment should be considered, beginning with the loading dose and maintenance dose (see section 4.2).

Treatment discontinuation for gMG

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

Treatment discontinuation for NMOSD

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

Switch from eculizumab to ravulizumab

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

Sodium content

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

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

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product 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. Based on the potential inhibitory effect of ravulizumab on complement-dependent cytotoxicity of rituximab, ravulizumab may reduce the expected pharmacodynamic effects of rituximab.
See section 4.2 for guidance in case of concomitant PE, PP, or IVIg treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception methods during treatment and 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 reactions with ravulizumab (intravenous formulation) are headache (26.6%), nasopharyngitis (17.5%), upper respiratory tract infection (16.8%), diarrhoea (14.2%), pyrexia (12.2%), nausea (12.2%), arthralgia (11.3%), fatigue (11.2%), back pain (10.4%), and abdominal pain (10.1%). The most serious adverse reactions are meningococcal infection (0.6%) including meningococcal sepsis and encephalitis meningococcal (see section 4.4).

Tabulated list of adverse reactions

Table 10 gives the adverse reactions observed from clinical trials and from post-marketing experience (intravenous formulations).
Adverse reactions are listed by MedDRA System Organ Class (SOC) and frequency, using the following convention: very common (≥ 1/ 10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from available data).

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

Table 10: Adverse reactions from clinical trials and postmarketing experience

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

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

[b] Gonococcal infection includes disseminated gonococcal infection

[c] Estimated from postmarketing experience

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

Description of selected adverse reactions

Meningococcal infection/sepsis/encephalitis
Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, < 1 % of patients developed serious meningococcal infections while receiving treatment with ravulizumab; all were adult patients with PNH or NMOSD who had been vaccinated.
Please refer to section 4.4 for information on prevention and treatment of suspected meningococcal infection. In patients treated with ravulizumab, meningococcal infections have presented as meningococcal sepsis and encephalitis meningococcal. Patients should be informed of the signs and symptoms of meningococcal infection and advised to seek medical care immediately.

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

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

Paediatric population

Paroxysmal nocturnal haemoglobinuria (PNH)
In paediatric PNH patients (aged 9 to 17 years old) enrolled in the paediatric PNH Study (ALXN1210-PNH-304), the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reactions reported in paediatric PNH patients were abdominal pain and nasopharyngitis, which occurred in 2 patients (15.4%).

Atypical haemolytic uremic syndrome (aHUS)
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 (32.3%).

Generalised Myasthenia Gravis (gMG)
Ravulizumab has not been studied in paediatric patients with gMG.

Neuromyelitis Optica Spectrum Disorder (NMOSD)
Ravulizumab has not been studied in paediatric patients with NMOSD.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, 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 membrane attack complex [MAC or C5b-9]) and preventing the generation of the

C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Pharmacodynamic effects

Following ravulizumab treatment in both adult and paediatric complement inhibitor-naïve patients and eculizumab-experienced patients with PNH in Phase 3 studies, immediate, complete and sustained inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all patients. Immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS, in adult patients with gMG, and in adult patients with NMOSD by the end of the first infusion and throughout the primary treatment period.
The extent and duration of the pharmacodynamic response in patients with PNH, aHUS, gMG, or NMOSD were exposure dependent for ravulizumab. Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition. In gMG, terminal complement activation leads to MAC deposition at the neuromuscular junction and impairment of neuromuscular transmission. In NMOSD, terminal complement activation leads to MAC formation and C5a-dependent inflammation, astrocyte necrosis, and damage to surrounding glial cells and neurons.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria (PNH)
The safety and efficacy of ravulizumab in adult patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:
- a complement inhibitor-naïve study in adult patients with PNH who were naïve to complement inhibitor treatment,
- an eculizumab-experienced study in adult patients with PNH who were clinically stable after having been treated with eculizumab for at least the previous 6 months.

Ravulizumab was dosed in accordance with the recommended dosing described in section 4.2 (4 infusions of ravulizumab over 26 weeks) while eculizumab was administered according to the approved dosing regimen of eculizumab of 600 mg every week for the first 4 weeks and 900 mg every 2 weeks (15 infusions over 26 weeks).
Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with ravulizumab or eculizumab or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.
There were no noteworthy differences in the demographic or baseline characteristics between the ravulizumab and eculizumab treatment groups in either of the Phase 3 studies. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 studies.

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

The complement inhibitor-naïve study was a 26-week, multicentre, open-label, randomised, active-controlled, Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry. 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 11 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 11: Baseline characteristics in the complement inhibitor-naïve study

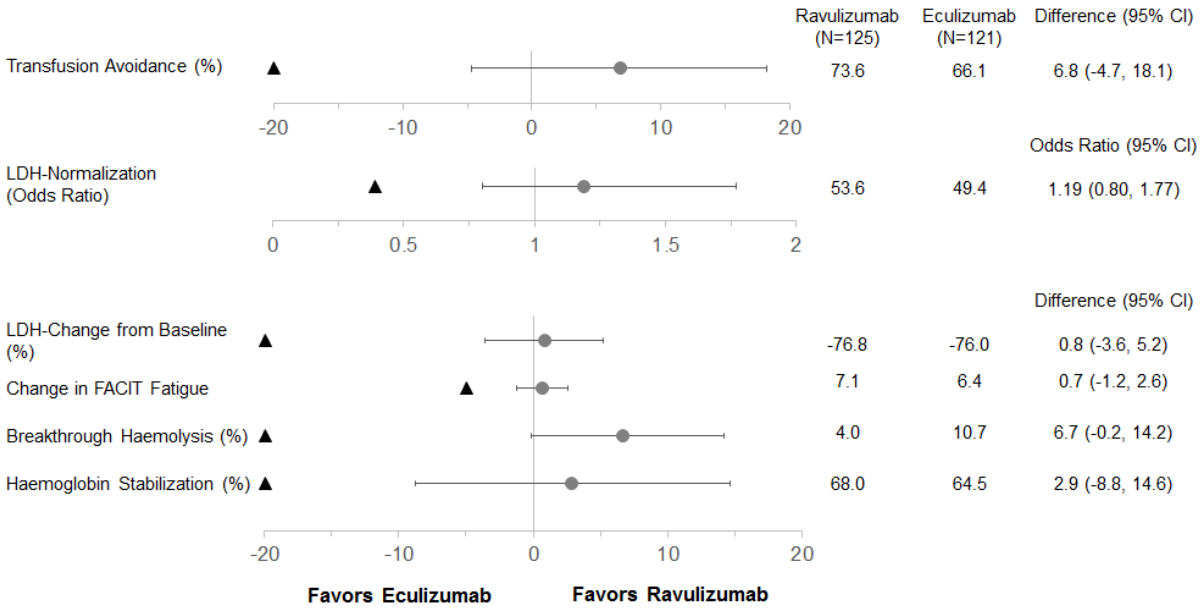
Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	37.9 (14.90) 34.0 15, 81	39.6 (16.65) 36.5 13, 82
Age (years) at first infusion in study	Mean (SD) Median Min, max	44.8 (15.16) 43.0 18, 83	46.2 (16.24) 45.0 18, 86
Sex (n, %)	Male Female	65 (52.0) 60 (48.0)	69 (57.0) 52 (43.0)
Pre-treatment LDH levels	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0
Number of patients with packed red blood cell (pRBC) transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
Units of pRBC transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Total PNH RBC clone size	Median	33.6	34.2
Total PNH granulocyte clone size	Median	93.8	92.4
Patients with any PNH conditions[a] prior to informed consent Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[b]	n (%)	121 (96.8) 103 (82.4) 81 (64.8) 41 (32.8) 19 (15.2) 7 (5.6) 3 (2.4) 27 (21.6)	120 (99.2) 105 (86.8) 75 (62.0) 38 (31.4) 11 (9.1) 6 (5.0) 4 (3.3) 13 (10.7)

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

The coprimary endpoints were transfusion avoidance, and haemolysis as directly measured by normalisation of LDH levels (LDH levels ≤ 1 × ULN; the ULN for LDH is 246 U/L). Key secondary endpoints included the percent change from baseline in LDH levels, change in quality of life (FACIT-Fatigue), the proportion of patients with breakthrough haemolysis and proportion of patients with stabilised haemoglobin.

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

Figure 1: Analysis of coprimary and secondary endpoints – full analysis set (complement inhibitor-naïve study)



Note: The black triangle indicates the non-inferiority margins, and grey dots indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

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

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

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 12 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 12: Baseline characteristics in the eculizumab-experienced study

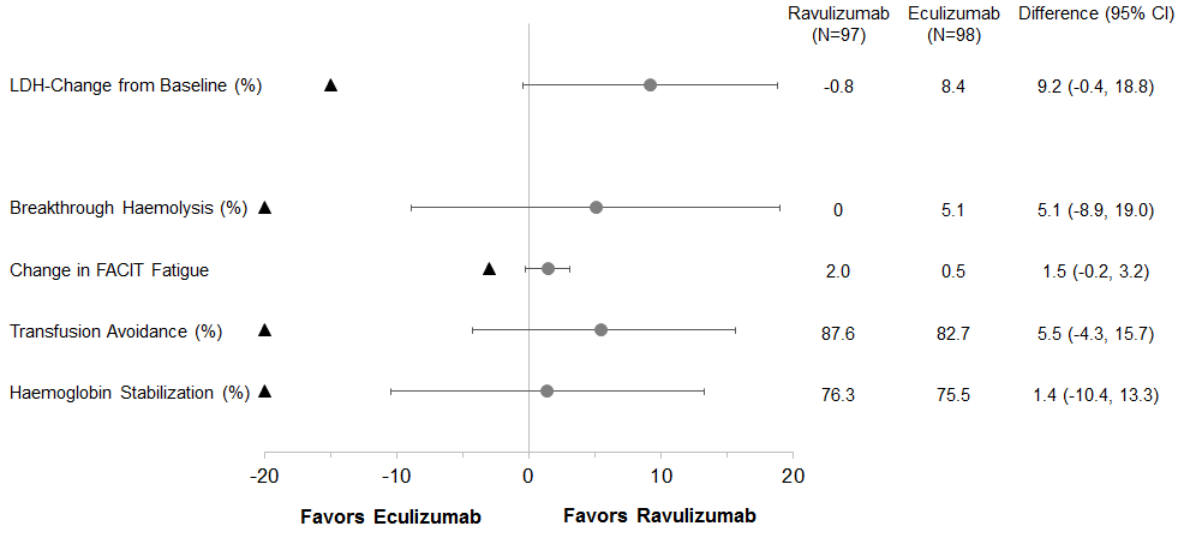
Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	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	n (%)	90 (92.8)	96 (98.0)
Anaemia		64 (66.0)	67 (68.4)
Haematuria or haemoglobinuria		47 (48.5)	48 (49.0)
Aplastic anaemia		34 (35.1)	39 (39.8)
Renal failure		11 (11.3)	7 (7.1)
Myelodysplastic syndrome		3 (3.1)	6 (6.1)
Pregnancy complication		4 (4.1)	9 (9.2)
Other[b]		14 (14.4)	14 (14.3)

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

The primary endpoint was 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 grey dot indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval.

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

Atypical haemolytic uremic syndrome (aHUS)

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

The adult study was a multicentre, single arm, Phase 3 study conducted in patients with documented aHUS who were naïve to complement inhibitor treatment prior to study entry and had evidence of thrombotic microangiopathy (TMA). The study consisted of a 26-week initial evaluation period and patients were allowed to enter an extension period for up to 4.5 years.
A total of 58 patients with documented aHUS were enrolled. Enrolment criteria excluded patients presenting with TMA due to 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 13 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the full analysis set.

Table 13: Baseline characteristics in the adult study

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

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

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

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week initial evaluation period as shown in Table 14.

Table 14: 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 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 (7 to 169 days). An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 118.52 × 10^9/L at baseline to 240.34 × 10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the initial evaluation period (26 weeks). Similarly, mean LDH value decreased from baseline over the first 2 months of treatment and was sustained over the duration of the initial evaluation period (26 weeks).

Of the patients who presented at CKD Stage 5, 67.6% (23/34) showed an improvement of 1 or more CKD Stages. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week initial evaluation period. 17 of the 29 patients who required dialysis at study entry were able to discontinue dialysis by the end of the available follow-up while 6 of 27 patients who were off dialysis at baseline were on dialysis at last available follow-up. Table 15 summarises the secondary efficacy outcomes for Study ALXN1210-aHUS-311.

Table 15: 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		
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)*	0.714 (0.587, 0.842)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	32/47	
Proportion (95% CI)*	0.681 (0.529, 0.809)	
Worsened[b]		
m/n	2/13	
Proportion (95% CI)*	0.154 (0.019, 0.454)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=48)	Change from baseline (n=47)
Mean (SD)	51.83 (39.162)	34.80 (35.454)
Median	40.00	29.00

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

Generalised Myasthenia Gravis (gMG)

Study in adult patients with gMG

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

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

A total of 162 (92.6%) patients completed the 26-week Randomised-Controlled Period of Study ALXN1210-MG-306. The baseline characteristics of patients are presented in Table 16. The majority (97%) of patients included in the study had been treated with at least one immunomodulatory therapy including immunosuppressant therapies, PE/PP, or IVIg in the last two years prior to enrolment.

Table 16: Baseline disease characteristics in study ALXN1210-MG-306

Parameter	Statistics	Placebo (N = 89)	Ravulizumab (N = 86)
Sex	n (%)		
Male		44 (49.4)	42 (48.8)
Female		45 (50.6)	44 (51.2)
Age at first dose of study drug (years)	Mean (SD) (min, max)	53.3 (16.05) (20, 82)	58.0 (13.82) (19, 79)
Elderly (≥ 65 years of age) at study entry	n (%)	24 (27.0)	30 (34.9)
Duration of MG since diagnosis (years)	Mean (SD) (min, max) Median	10.0 (8.90) (0.5, 36.1) 7.6	9.8 (9.68) (0.5, 39.5) 5.7
Baseline MG-ADL Score	Mean (SD) (min, max) Median	8.9 (2.30) (6.0, 15.0) 9.0	9.1 (2.62) (6.0, 24.0) 9.0
Baseline QMG Score	Mean (SD) (min, max) Median	14.5 (5.26) (2.0, 27.0) 14.0	14.8 (5.21) (6.0, 39.0) 15.0
Baseline MGFA classification	n (%)		
Class II (mild weakness)		39 (44)	39 (45)
Class III (moderate weakness)		45 (51)	41 (48)
Class IV (severe weakness)		5 (6)	6 (7)
Any prior intubation since diagnosis (MGFA Class V)	n (%)	9 (10.1)	8 (9.3)
Number of patients with prior MG crisis since diagnosis[a]	n (%)	17 (19.1)	21 (24.4)
Number of stable immunosuppressant therapies[b] at study entry	n (%)		
0		8 (9.0)	10 (11.6)
1		34 (38.2)	40 (46.5)
⩾ 2		47 (52.8)	36 (41.9)

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

[b] Immunosuppressant therapies include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus.

Abbreviations: Max = maximum; min = minimum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis; SD = standard deviation

The primary endpoint was the change from baseline to Week 26 in the MG-ADL total score.

The secondary endpoints, also assessed changes from baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score, the proportion of patients with improvements of at

least 5 and 3 points in the QMG and MG-ADL total scores, respectively, as well as changes in quality-of-life assessments.

Ravulizumab demonstrated a statistically significant change in the MG-ADL total score as compared to placebo. Primary and secondary endpoint results are presented in Table 17.

Table 17: Analysis of primary and secondary efficacy endpoints

Efficacy Endpoints at Week 26	Placebo (N = 89) LS Mean (SEM)	Ravulizumab (N = 86) LS Mean (SEM)	Statistic for Comparison	Treatment Effect (95% CI)	p-value (Using Mixed Effect Repeated Measures)
MG-ADL	-1.4 (0.37)	-3.1 (0.38)	Difference in change from baseline	-1.6 (-2.6, -0.7)	0.0009
QMG	-0.8 (0.45)	-2.8 (0.46)	Difference in change from baseline	-2.0 (-3.2, -0.8)	0.0009
MG-QoL15r	-1.6 (0.70)	-3.3 (0.71)	Difference in change from baseline	-1.7 (-3.4, 0.1)	0.0636
Neuro-QoL-fatigue	-4.8 (1.87)	-7.0 (1.92)	Difference in change from baseline	-2.2 (-6.9, 2.6)	0.3734[a]

[a] The endpoint was not formally tested for statistical significance; a nominal p-value was reported.
Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QoL15r = Revised Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL-fatigue = Neurological Quality of Life Fatigue; QMG = Quantitative Myasthenia Gravis; SEM = standard error of mean.

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

Table 18 presents an overview of the patients with clinical deterioration and patients requiring rescue therapy over the 26-week Randomised-Controlled Period.

Table 18: Clinical deterioration and rescue therapy

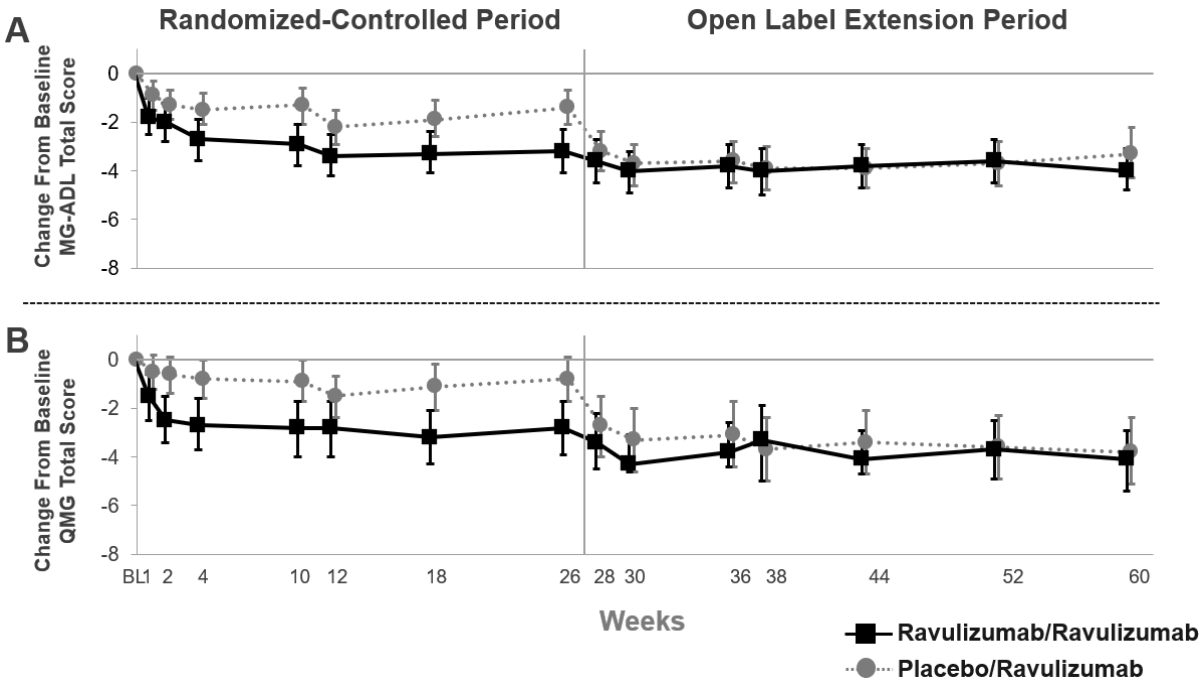
Variable	Statistic	Placebo (N = 89)	Ravulizumab (N = 86)
Total number of patients with clinical deterioration	n (%)	15 (16.9)	8 (9.3)
Total number of patients requiring rescue therapy[a]	n (%)	14 (15.7)	8 (9.3)

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

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

In patients who initially received ULTOMIRIS during the Randomised-Controlled Period and continued to receive ULTOMIRIS during the first 34-weeks of the Open-Label Extension Period, the treatment effect was sustained (Figure 3). In patients who initially received placebo during the 26-week Randomised-Controlled Period and initiated treatment with ULTOMIRIS during the Open-Label Extension Period, a rapid and sustained treatment response (Figure 3), was observed.

Figure 3: Change from randomised-controlled period baseline in MG-ADL total score (A) and QMG total score (B) through week 60 (mean and 95% CI)



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

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

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Study in adult patients with NMOSD

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

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

Patients included in the study had a mean age of 47.4 years (ranging from 18 to 74 years) and most of them were female (90%). Median age at NMOSD initial clinical presentation was of 42.5 years, ranging from 16 to 73 years. Baseline disease characteristics are shown in Table 19.

Table 19: Patient disease history and baseline characteristics in study ALXN1210-NMO-307

Variable	Statistic	ALXN1210-NMO-307 Ravulizumab (N = 58)
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Mean (SD)	5.2 (6.38)
	Median	2.0
	Min, max	0.19, 24.49
Historical ARR within 24 months prior to screening	Mean (SD)	1.87 (1.59)
	Median	1.44
	Min, max	0.5, 6.9
Baseline HAI score	Mean (SD)	1.2 (1.42)
	Median	1.0
	Min, max	0, 7
Baseline EDSS score	Mean (SD)	3.30 (1.58)
	Median	3.25
	Min, max	0.0, 7.0
Any historical rituximab use	n (%)	21 (36.2)
Number of patients receiving stable corticosteroids only at study entry	n (%)	12 (20.7)
Number of patients not receiving any IST at study entry	n (%)	30 (51.7)

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

The primary endpoint of Study ALXN1210-NMO-307 was the time to first adjudicated on-trial relapse as determined by an independent adjudication committee. No adjudicated on-trial relapse was observed in ravulizumab-treated patients during the Primary Treatment Period. All ravulizumab-treated patients remained relapse free over the median follow-up of 90.93 weeks. Ravulizumab-treated patients experienced consistent relapse-free primary endpoint result with or without concomitant IST treatment.

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

Paediatric population

Paroxysmal nocturnal haemoglobinuria (PNH)

Study in paediatric patients with PNH (ALXN1210-PNH-304)

The paediatric study (ALXN1210-PNH-304) is a multicentre, open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor-naïve paediatric patients with PNH.
From interim results, a total of 13 PNH paediatric patients completed ravulizumab treatment during the primary evaluation period (26 weeks) of Study ALXN1210-PNH-304. Five of the 13 patients had never been treated with a complement inhibitor and 8 patients received treatment with eculizumab prior to study entry.

Most of the patients were between 12 years and 17 years of age at first infusion (mean: 14.4 years), with 2 patients under 12 years old (11 years and 9 years old). Eight of the 13 patients were female. Mean weight at baseline was 56 kg, ranging from 37 to 72 kg. Table 20 presents the baseline disease history and characteristics of the paediatric patients enrolled in Study ALXN1210-PNH-304.

Table 20: Disease history and characteristics at baseline (full analysis set)

Variable	Complement inhibitor-naïve patients (N = 5)	Eculizumab-experienced patients (N = 8)
Total PNH RBC clone size (%)	(N = 4)	(N = 6)
Median (min, max)	40.05 (6.9, 68.1)	71.15 (21.2, 85.4)
Total PNH granulocyte clone size (%)		
Median (Min, max)	78.30 (36.8, 99.0)	91.60 (20.3, 97.6)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	2 (40.0)	2 (25.0)
Number of pRBC/whole blood transfusions within 12 months prior to first dose		
Total	10	2
Median (min, max)	5.0 (4, 6)	1.0 (1, 1)
Units of pRBC/whole blood transfused within 12 months prior to first dose		
Total	14	2
Median (min, max)	7.0 (3, 11)	2.0 (2, 2)
Patients with any PNH-associated conditions prior to informed consent, n (%)	5 (100)	8 (100)
Anaemia	2 (40.0)	5 (62.5)
Haematuria or haemoglobinuria	2 (40.0)	5 (62.5)
Aplastic anaemia	3 (60.0)	1 (12.5)
Renal failure	2 (40.0)	2 (25.0)
Other[a]	0	1 (12.5)
Pre-treatment LDH levels (U/L)		
Median (min, max)	588.50 (444, 2269.7)	251.50 (140.5, 487)

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

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

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

Based on body weight, patients received a loading dose of ravulizumab on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on eculizumab therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of eculizumab.

The weight-based dose regimen of ravulizumab provided immediate, complete, and sustained inhibition of terminal complement throughout the 26-week primary evaluation period regardless of prior experience with eculizumab. Following initiation of ravulizumab treatment, steady-state therapeutic serum concentrations of ravulizumab were achieved immediately after the first dose and maintained throughout the 26-week primary evaluation period in both cohorts. There were no breakthrough haemolysis events in the study and no patients had post-baseline free C5 levels above 0.5 µg/mL. Mean percent change from baseline in LDH was -47.91% on Day 183 in the complement inhibitor-naïve cohort and remained stable in the eculizumab-experienced cohort during the 26-week primary evaluation period. Sixty percent (3/5) of complement inhibitor-naïve patients and 75% (6/8) of eculizumab-experienced patients achieved haemoglobin stabilisation by Week 26 respectively. Transfusion-avoidance was reached by 84.6% (11/13) of patients during the 26-week primary evaluation period.

These interim efficacy results are presented in Table 21 below.

Table 21: Interim efficacy outcomes from the paediatric study in PNH patients (ALXN1210-PNH-304) - 26-week primary evaluation period

End Point	Ravulizumab (Naïve, N = 5)	Ravulizumab (Switch, N = 8)
LDH- Percent change from Baseline Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion Avoidance Percentage (95% CI)	60.0 (14.66, 94.73)	100.0 (63.06, 100.00)
Haemoglobin Stabilisation Percentage (95% CI)	60.0 (14.66, 94.73)	75 (34.91, 96.81)
Breakthrough Haemolysis (%)	0	0

Abbreviations: LDH = lactate dehydrogenase

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

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

Study in paediatric patients with aHUS (ALXN1210 aHUS 312)

The paediatric study is a 26-week ongoing, multicentre, 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 22 presents the baseline characteristics of the paediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 22: 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: 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 23.

Table 23: 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 × 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 for platelet count normalisation, 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for LDH normalisation, 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 24 summarises the secondary efficacy results for Study ALXN1210-aHUS-312.

Table 24: 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		
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	80.0

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.

Generalised myasthenia gravis (gMG)

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 the treatment of myasthenia gravis. See 4.2 for information on paediatric use.

Neuromyelitis optica spectrum disorder (NMOSD)

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 the treatment of NMOSD. See 4.2 for information on paediatric use.

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]) central volume and volume of distribution at steady state for adult and paediatric patients with PNH or aHUS and adult patients with gMG or NMOSD are presented in Table 25.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolised in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in adult and paediatric patients with PNH, adult and paediatric patients with aHUS, and adult patients with gMG or NMOSD are presented in Table 25.

Table 25: Estimated central volume, distribution, biotransformation and elimination parameters following ravulizumab administration

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

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

Linearity/non-linearity

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

Special populations

Weight
Body weight is a significant covariate in patients with PNH, aHUS, gMG, or NMOSD resulting in lower exposures in heavier patients. Weight-based dosing is proposed in section 4.2, Table 1, Table 3 and Table 4.

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Polysorbate 80
Arginine
Sucrose
Water for injections

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

18 months.

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.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

30 months.

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 6 hours at room temperature.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Pack size of one vial.

Ultomiris 300 mg/3 mL concentrate for solution for infusion

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

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

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

Ultomiris 300 mg/30 mL concentrate for solution for infusion

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

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only.

Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

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

Aseptic technique must be used.

Prepare Ultomiris concentrate for solution for infusion as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section 4.2.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9 %) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 50 mg/mL.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2 °C-8 °C. If stored at 2 °C-8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to the Table 6 and Table 7 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C – 8 °C or 4 hours at room temperature taking into account the expected infusion time.

Table 26: Loading dose administration reference table for Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

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

[a] Body weight at time of treatment.

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

Table 27: Maintenance dose administration reference table for Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

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

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

Table 28: Supplemental dose administration reference table for Ultomiris 300 mg/3 mL and 1 100 mg/11 mL concentrates for solution for infusion

Body weight range (kg)[a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
⩾ 40 to < 60	600	6	6	12
	1,200	12	12	24
	1,500	15	15	30
⩾ 60 to < 100	600	6	6	12
	1,500	15	15	30
	1,800	18	18	36
⩾ 100	600	6	6	12
	1,500	15	15	30
	1,800	18	18	36

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

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

Ultomiris 300 mg/30 mL concentrate for solution for infusion

This medicinal product requires dilution to a final concentration of 5 mg/mL.

Aseptic technique must be used.

Prepare Ultomiris concentrate for solution for infusion as follows:
1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section 4.2.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9 %) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 5 mg/mL.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2 °C-8 °C. If stored at 2 °C-8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to the Table 8 and Table 9 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 29: Loading dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion

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	1,200	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 30: Maintenance dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion

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	2,100	210	210	420
≥ 30 to < 40	2,700	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.

Table 31: Supplemental dose administration reference table for Ultomiris 300 mg/30mL concentrate for solution for infusion

Body weight range (kg)[a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
⩾ 40 to < 60	600	60	60	120
	1,200	120	120	240
	1,500	150	150	300
⩾ 60 to < 100	600	60	60	120
	1,500	150	150	300
	1,800	180	180	360
⩾ 100	600	60	60	120
	1,500	150	150	300
	1,800	180	180	360

[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. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/001
EU/1/19/1371/002
EU/1/19/1371/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 245 mg solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultomiris is a formulation of ravulizumab produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.
Each pre-filled cartridge contains 245 mg of ravulizumab in 3.5 mL solution (70 mg/mL).
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection (on-body injector)

Translucent, clear to yellowish colour, pH 7.4 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Ultomiris is indicated in the treatment of adult patients 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.

4.2 Posology and method of administration

Ravulizumab solution for injection is intended for use under the guidance and supervision of a physician experienced in the management of patients with haematological or renal disorders.

Posology

Adult patients with PNH and aHUS

Ravulizumab intravenous formulation loading dose
For complement-inhibitor treatment-naïve patients or patients switching treatment from eculizumab, a weight-based loading dose using ravulizumab intravenous formulation is required prior to the initiation of ravulizumab subcutaneous formulation maintenance therapy. For weight-based dosing information for the intravenous loading dose, see section 4.2 of the Ultomiris concentrate for solution for infusion summary of product characteristics (SmPC).

Ravulizumab subcutaneous formulation maintenance doses
The recommended maintenance dose in adult patients with PNH or aHUS with a body weight greater than or equal to 40 kg is 490 mg, administered once weekly, starting 2 weeks after loading dose.

The dosing schedule of ravulizumab solution for injection is allowed to occasionally vary by ± 1 day of the scheduled dose day but the subsequent dose should be administered according to the original schedule.

Treatment initiation instructions in patients who are complement-inhibitor treatment-naïve or switching treatment from ravulizumab intravenous formulation or eculizumab are shown in Table 1.

Table 1: Ravulizumab treatment initiation instructions

Population	Weight-based ravulizumab intravenous formulation loading dose [a]	Time of first ravulizumab subcutaneous formulation maintenance dose
Not currently on ravulizumab intravenous formulation or eculizumab treatment	At treatment start	2 weeks after ravulizumab intravenous loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after ravulizumab intravenous loading dose
Currently treated with ravulizumab intravenous formulation	Not applicable	8 weeks after last ravulizumab intravenous maintenance dose

[a] for weight-based ravulizumab intravenous loading dose in patients with body weight ≥ 40 kg, refer to the ravulizumab intravenous formulation SmPC

Administration of PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) or intravenous human immunoglobulin (IVIg) 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 thrombotic microangiopathy (TMA) manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy (see section 4.4).

Treatment switch from ravulizumab subcutaneous formulation to ravulizumab intravenous formulation
Patients treated with ravulizumab subcutaneous formulation maintenance treatment have the possibility to switch to ravulizumab intravenous formulation in agreement with their treating physician. See Ultomiris concentrates for solution for infusion Summary of Product Characteristics (SmPC) for further details.

Treatment initiation instructions of ravulizumab intravenous formulation in patients treated with ravulizumab subcutaneous formulation are shown in Table 2.

Table 2: Ravulizumab intravenous formulation treatment initiation instructions

Population	Weight-based ravulizumab intravenous loading dose	Time of first ravulizumab intravenous weight-based maintenance dose
Currently treated with ravulizumab subcutaneous formulation	Not applicable	1 week after last ravulizumab subcutaneous dose

Special populations

Elderly
No dose adjustment is required for patients with 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
No dose adjustment is required for patients with renal impairment (see section 5.2).

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

Paediatric population
The safety and efficacy of ravulizumab subcutaneous formulation in children below 18 years of age have not been established. No data are available. Ravulizumab subcutaneous formulation should not be used in children below 18 years of age.

Method of administration

For subcutaneous injection.

Ravulizumab solution for injection may be self-administered or administered by a caregiver or healthcare professional after appropriate training.

The solution for injection in cartridge is administered with single-use on-body injectors.

This medicinal product is for subcutaneous administration into the abdomen, thigh, or outer area of the upper arm region. Injection sites should be rotated, and injections should not be given into areas where the skin is tender, bruised, red or hard. Avoid injecting into areas with scars or stretch marks.

The 490 mg dose of ravulizumab is delivered using two on-body delivery systems. Each on-body delivery system consists of one on-body injector and one pre-filled cartridge containing 245 mg of ravulizumab. The two on-body delivery systems can be administered concurrently or sequentially. Each injection is delivered in approximately 10 minutes.

Each pre-filled cartridge and on-body injector of Ultomiris is intended for single use only.

Ravulizumab solution for injection in cartridge is not intended for intravenous administration.

Ultomiris 245 mg solution for injection in cartridge does not require dilution prior to administration.

Detailed instructions for administration:
1. Remove two cartons from the refrigerator. Two on-body injectors and two cartridges are required for a full dose.
2. Inspect the packaging. The on-body injectors or cartridges should not be used if they have been dropped or appear to be broken or damaged.
3. Wait at least 45 minutes for the on-body injectors and pre-filled cartridges in the cartons to naturally reach room temperature. Do not return to the refrigerator. Discard after 3 days at room temperature (20°C - 25°C).
4. Before administration, visually inspect the solution. The solution should not be injected if it contains flakes or particles or is cloudy or discoloured.
5. Load the first clean cartridge into the first on-body injector and secure in place before closing the cartridge door on the injector. Do not insert the cartridge more than 5 minutes before the injection to avoid drying out the solution.

6. Peel away the adhesive backing of the first on-body injector and apply the on-body injector onto the clean, dry, chosen injection site(s) (thigh, abdomen, or upper arm).
7. Start the injection by firmly pressing and releasing the blue start button.
8. Repeat for the second on-body injector.
9. Do not remove until the injection is complete (signalled by the green status light, 3 beeping sounds, and the white plunger filling the medicine window).

For detailed instructions on how to use the on-body injector, see the instructions for use provided with the on-body injector.

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 or fatal meningococcal infections/sepsis have been reported in patients treated with ravulizumab and in patients treated with other terminal complement inhibitors. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. Physicians should provide patients with a patient information brochure and a Patient card.

Immunisation

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

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

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

Infusion-related reactions

Administration of ravulizumab may result in systemic infusion-related reactions and allergic or hypersensitivity reactions, including anaphylaxis (see section 4.8).

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

Allergies to acrylic adhesives

The on-body injector of ravulizumab subcutaneous formulation uses acrylic adhesive. For patients with a known allergy to acrylics adhesive, use of this product may result in an allergic reaction. Premedication can be considered and/or supportive measures should be instituted if signs of allergy appear.

Treatment discontinuation for PNH

If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of 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 thrombotic microangiopathy (TMA) recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.

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

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

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

If TMA complications occur after ravulizumab discontinuation, reinitiation of ravulizumab should be considered, beginning with the loading dose and maintenance dose described in section 4.2.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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 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

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with ravulizumab intravenous or subcutaneous formulation are headache (28.3%), injection site reactions (25%), nasopharyngitis (19.8%), upper respiratory tract infection (18.1%), pyrexia (15.6%), diarrhoea (15.2%), nausea (13.2%), abdominal pain (12.2%), fatigue (11.2%), arthralgia (11.0%), and back pain (10.3%). The most serious adverse reactions in patients are meningococcal infection (0.3%) and meningococcal sepsis (0.1%).

The safety profile of ravulizumab subcutaneous formulation appeared similar to ravulizumab intravenous formulation.

Tabulated list of adverse reactions

Adverse reactions observed from clinical trials and post marketing experience (intravenous or subcutaneous formulation) are displayed by System Organ Class and preferred term in Table 3 below using the MedDRA frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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

Table 3: Adverse reactions from clinical trials and postmarketing experience

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

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

[b] Gonococcal infection includes disseminated gonococcal infection
[c] Hypersensitivity is a group term for Preferred Term drug hypersensitivity with related causality and Preferred Term hypersensitivity.
[d] Estimated from post-marketing experience with intravenous formulation
[e] Occurred with subcutaneous administration of ravulizumab.
[f] Injection Site Reactions include the following injection associated terms during or within 24 hours post subcutaneous injection: injection reactions (Not otherwise specified), erythema, rash, swelling, pruritus, ecchymosis, pain, haematoma, induration, bruise, urticaria, and inflammation.

Description of selected adverse reactions

Meningococcal infections/sepsis
Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 0.4% of the patients developed serious meningococcal infections/sepsis while receiving treatment with ravulizumab. All were adult patients with PNH who had been vaccinated. All patients recovered while continuing treatment with ravulizumab. Please refer to section 4.4 for information on prevention and treatment of suspected meningococcal infection. In patients treated with ravulizumab, meningococcal infections presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek medical care immediately.

Infusion-related reactions
In clinical trials, infusion-related reactions were common (≥1%). They were mild to moderate in severity and transient (e.g., lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity [allergic reaction], dysgeusia [bad taste], and drowsiness). These reactions did not require discontinuation of Ultomiris.

Immunogenicity
In adult PNH patient studies (N = 475), paediatric PNH study (N=13), aHUS studies (N = 89), 2 (0.3%) cases of development of treatment emergent anti-drug antibodies have been reported with ravulizumab IV (1 adult patient with PNH and 1 adult patient with aHUS). These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events. In the ravulizumab subcutaneous study in PNH (N=128), no treatment-emergent anti-drug antibodies were observed.

Injection site reactions
In clinical trials for PNH with subcutaneous administration of ravulizumab via the on-body-injector, local injection site reactions were reported in 25% of the participants. Injection site reactions included erythema, rash, swelling, pruritus, ecchymosis, pain, haematoma, induration, bruise, urticaria, and inflammation at the injection site. These reactions were mild in severity and transient and did not require discontinuation of ravulizumab.

Paediatric population

The safety and efficacy of ravulizumab subcutaneous formulation in children below 18 years of age 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA43

Mechanism of action

Ravulizumab is a monoclonal antibody IgG2/4K that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Pharmacodynamic effects

Following ravulizumab subcutaneous treatment, immediate and complete terminal complement inhibition was observed in adult eculizumab-experienced patients with PNH by the end of the first dose and was sustained throughout the 1-year treatment period.
The PD results following ravulizumab SC treatment are consistent with prior results in PNH and aHUS adult patients treated with ravulizumab IV.
The extent and duration of the pharmacodynamic response were exposure-dependent in patients with PNH, or aHUS following ravulizumab treatment. Free C5 levels of < 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Clinical efficacy and safety

Subcutaneous formulation

Study of subcutaneous administration in adult patients with PNH (ALXN1210-PNH-303)

Subcutaneous administration of ravulizumab was assessed in a multi-centre, randomized, open-label, Phase 3 study conducted in adult patients with PNH who were clinically stable (LDH ≤1.5x ULN) after having been treated with eculizumab for at least three months prior to study entry. The study enrolled 136 patients, of which 129 patients were included in the efficacy and safety analyses. The main outcome measure of Study ALXN1210-PNH-303 was the non-inferiority of C_{trough} of ravulizumab when administered subcutaneously (SC) via an on-body injector compared to ravulizumab administered intravenously (IV). The study was designed to bridge efficacy and safety data from ravulizumab intravenous to ravulizumab subcutaneous administration.

Patients who completed the 10-week randomized treatment period are followed for up to 172 weeks in the long-term Extension Period. During the Randomized Treatment Period, patients were stratified by weight group (≥ 40 kg to < 60 kg and ≥ 60 kg to < 100 kg) and randomized 2:1 to receive ravulizumab subcutaneous formulation or intravenous formulation. On Day 1, all patients received a weight-based ravulizumab intravenous loading dose. On Day 15, patients randomized to the ravulizumab subcutaneous formulation group received once weekly maintenance subcutaneous doses (490 mg), while patients randomized to the ravulizumab intravenous formulation group received the approved weight-based intravenous maintenance dose. Following the Randomized Treatment Period (on Day 71), patients who were randomized to the intravenous formulation group switched to receive 490 mg of ravulizumab subcutaneous formulation weekly through the end of the Extension Period.

The mean total PNH RBC clone size was 48.35%, with a mean total PNH granulocyte clone size of 77.22% and a mean total PNH monocyte clone size of 80.18% at baseline. Ninety two percent of the patients had documented PNH-associated conditions that were diagnosed prior to informed consent. Overall, the disease history and baseline characteristics were well balanced between the two treatment groups. Table 4 presents the baseline characteristics of the PNH patients enrolled in Study ALXN1210-PNH-303.

Table 4: Baseline characteristics (study ALXN1210-PNH-303)

Variable	Ravulizumab (IV) (N = 45)	Ravulizumab (SC) (N = 84)	Total (N = 129)
Sex, n (%)			
Male	20 (44.4)	40 (47.6)	60 (46.5)
Female	25 (55.6)	44 (52.4)	69 (53.5)
Race, n (%)			
White	29 (64.4)	63 (75.0)	92 (71.3)
Not Reported	6 (13.3)	13 (15.5)	19 (14.7)
Black or African American	4 (8.9)	3 (3.6)	7 (5.4)
Asian	2 (4.4)	0	2 (1.6)
Unknown or other	3 (6.7)	5 (6.0)	8 (6.2)
American Indian or Alaska Native	1 (2.2)	0	1 (0.8)
Age (years) at Informed Consent			
Mean (SD)	46.4 (13.22)	45.3 (14.47)	45.7 (14.00)
Median	44.0	42.5	44.0
Min, Max	24, 77	18, 79	18, 79
Age (years) at Informed Consent Category, n (%)			
>65	4 (8.9)	9 (10.7)	13 (10.1)
Baseline Weight (kg)			
Mean (SD)	73.68 (12.655)	72.52 (12.611)	72.92 (12.589)
Median	73.00	72.15	72.30
Min, Max	52.0, 98.4	43.5, 98.0	43.5, 98.4
Baseline Weight (kg) Category, n (%)			
≥ 40 to < 60	8 (17.8)	13 (15.5)	21 (16.3)
≥ 60 to < 100	37 (82.2)	71 (84.5)	108 (83.7)
Baseline LDH (U/L)			
Mean (SD)	267.4 (83.47)	270.0 (174.53)	269.1 (148.83)
Median	253.0	236.0	240.0
Min, Max	90, 519	125, 1260	90, 1260

Percentages are based on the total number of patients. Patients can be counted in more than one category for race. A total of 7 patients were excluded from the analyses due to source document deviations.

In Study ALXN1210-PNH-303, treatment with ravulizumab subcutaneous formulation achieved PK non-inferiority compared with ravulizumab intravenous formulation treatment for the serum ravulizumab C_{trough} at Day 71, with a geometric Least Squares Mean ratio of 1.257 (90% CI: 1.160, 1.361). Serum free C5 concentrations were maintained below the target threshold (< 0.5 µg/mL) in all patients.

Table 5: Efficacy outcomes at 10 weeks (day 71) of randomized treatment period and through 1 year of ravulizumab subcutaneous formulation treatment

Efficacy outcomes at 10-week randomized treatment period			
Endpoints	**Statistic**	**Ravulizumab (IV) (N=45)**	**Ravulizumab (SC) (N=84)**
LDH – Percent Change from Baseline	Mean (SD) Range	(N=43) 5.73% (29.716) -42.6, 174.1	(N=82) 2.57% (33.883) -82.6, 179.5
Breakthrough Haemolysis [a]	n (%) 95% CI	1 (2.2) 0.06, 11.77	1 (1.2) 0.03, 6.46
Transfusion Avoidance	n (%) 95% CI	39 (86.7) 73.21, 94.95	79 (94.0) 86.65, 98.04
Haemoglobin Stabilization	n (%) 95% CI	(N = 44) 36 (81.8) 67.29, 91.81	(N = 78) 73 (93.6) 85.67, 97.89
FACIT-Fatigue – Change from Baseline	Mean (SD) Range	(N = 44) -0.83 (7.378) -26.0, 15.4	(N = 80) 1.21 (7.882) -32.0, 33.0

Efficacy outcomes through 1 year of ravulizumab subcutaneous formulation treatment			
Endpoints	**Total N**	**Statistic**	**Ravulizumab (SC)**
LDH – Percent Change from Baseline	107	Mean (SD) 95% CI	0.92 (20.49) -3.004, 4.85
Breakthrough Haemolysis [a]	128	n (%) 95% CI	5 (3.9) 1.28, 8.88
Transfusion Avoidance	128	n (%) 95% CI	107 (83.6) 76.02, 89.55
Haemoglobin Stabilization	123	n (%) 95% CI	98 (79.7) 71.48, 86.39
FACIT-Fatigue – Change from Baseline	70	Mean (SD) 95% CI	2.6 (7.18) 0.86, 4.28

[a] Breakthrough haemolysis (BTH) is defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory. One patient in the IV group experienced BTH on Day 57. This patient did not have a free C5 sample obtained at the Day 57 visit; however, showed complete C5 control at all other sampling time points.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; FACIT= Functional Assessment of Chronic Illness Therapy; SC= subcutaneous; IV= intravenous

Overall, the efficacy of ravulizumab subcutaneous formulation was similar to that of ravulizumab intravenous formulation during the primary evaluation period. At Day 71, all patients in the ravulizumab intravenous formulation group were switched to subcutaneous administration for the remainder of the study. The efficacy was maintained through 1 year of treatment and there were no significant differences in safety between the ravulizumab subcutaneous formulation and ravulizumab intravenous formulation arms aside from injection site reactions associated with the subcutaneous route of administration (See section 4.8).

Results from the Treatment Administration Satisfaction Questionnaire (TASQ), a patient reported outcome questionnaire that scores treatment administration satisfaction, indicated that patients treated with the ravulizumab subcutaneous formulation experienced greater satisfaction with the subcutaneous route of administration than with the intravenous route of administration for eculizumab.

Intravenous formulation

Paroxysmal nocturnal haemoglobinuria (PNH)
The safety and efficacy of ravulizumab in adult patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:
- a complement-inhibitor naïve study in adult patients with PNH who were naïve to complement inhibitor treatment (Study ALXN1210-PNH-301).
- 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 (Study ALXN1210-PNH-302).

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

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

There were no noteworthy differences in the demographic or baseline characteristics between the ravulizumab and eculizumab treatment groups in either of the Phase 3 studies. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 studies.

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

The complement-inhibitor naïve study was a 26 week, multicentre, open-label, randomised, active-controlled, Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry. 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 6 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 6: Baseline characteristics in the complement-inhibitor naïve study

Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Age (years) at PNH diagnosis	Mean (SD)	37.9 (14.90)	39.6 (16.65)
	Median	34.0	36.5
	Min, max	15, 81	13, 82
Age (years) at first infusion in study	Mean (SD)	44.8 (15.16)	46.2 (16.24)
	Median	43.0	45.0
	Min, max	18, 83	18, 86
Sex (n, %)	Male	65 (52.0)	69 (57.0)
	Female	60 (48.0)	52 (43.0)
Pre-treatment LDH levels	Mean (SD)	1633.5 (778.75)	1578.3 (727.06)
	Median	1513.5	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	925	861
	Mean (SD)	9.0 (7.74)	8.6 (7.90)
	Median	6.0	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)

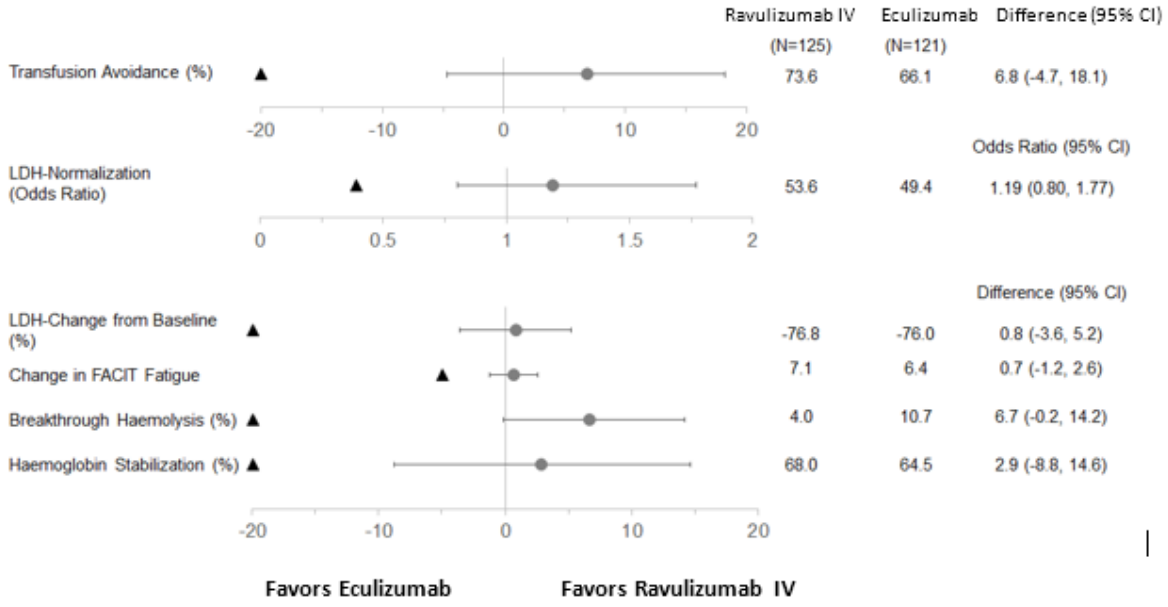
[a] Based on medical history.

[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 stabilised haemoglobin.

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

Figure 1: Analysis of coprimary and secondary endpoints – full analysis set (complement-inhibitor naïve study)



Note: The black triangle indicates the non-inferiority margins, and grey dots indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

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

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

PNH medical history was similar between ravulizumab IV and eculizumab treatment groups. The 12-month transfusion history was similar between ravulizumab IV 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 7 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 7: Baseline characteristics in the eculizumab-experienced study

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

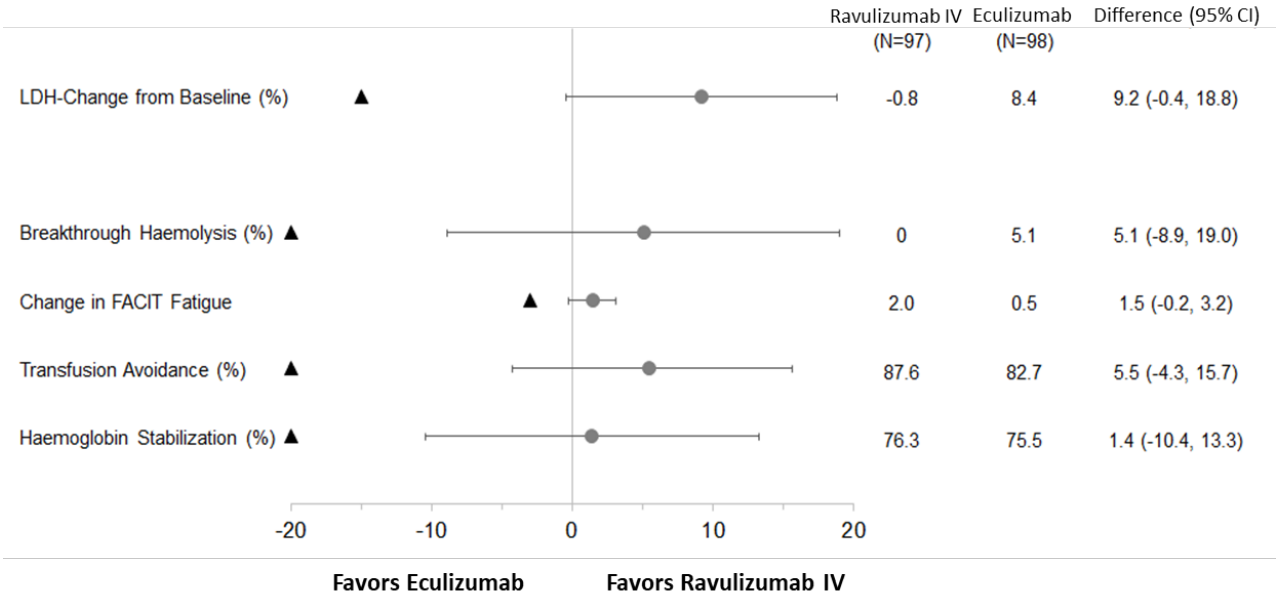
[a] Based on medical history.

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

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

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

Figure 2: Analysis of primary and secondary endpoints – full analysis set (eculizumab-experienced study)



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

Atypical haemolytic uremic syndrome (aHUS)

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

The adult study was a multicentre, single arm, Phase 3 study conducted in patients with documented aHUS who were naïve to complement inhibitor treatment prior to study entry and had evidence of 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 8 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the full analysis set.

Table 8: Baseline characteristics in the adult study

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

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

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

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week initial evaluation period as shown in Table 9.

Table 9: 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 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 (7 to 169 days). An increase in mean platelet count was observed rapidly after commencement of ravulizumab, increasing from 118.52 × 10^9/L at baseline to 240.34 × 10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the initial evaluation period (26 weeks). Similarly, mean LDH value decreased from baseline over the first 2 months of treatment and was sustained over the duration of the initial evaluation period (26 weeks).

Of the patients who presented at CKD Stage 5, 67.6% (23/34) showed an improvement of 1 or more CKD Stages. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week initial evaluation period. 17 of the 29 patients who required dialysis at study entry were able to discontinue dialysis by the end of the available follow-up while 6 of 27 patients who were off dialysis at baseline were on dialysis at last available follow-up. Table 10 summarises the secondary efficacy outcomes for Study ALXN1210aHUS-311.

Table 10: 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 Mean (SD) Median	237.96 (73.528) 232.00	114.79 (105.568) 125.00
LDH (U/L) serum Mean (SD) Median	194.46 (58.099) 176.50	-519.83 (572.467) -310.75
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period m/n proportion (95% CI)*	40/56 0.714 (0.587, 0.842)	
CKD stage shift from baseline, Day 183 Improved[a] m/n Proportion (95% CI)* Worsened[b] m/n Proportion (95% CI)*	32/47 0.681 (0.529, 0.809) 2/13 0.154 (0.019, 0.454)	
eGFR (mL/min/1.73 m^2), Day 183 Mean (SD) Median	Observed value (n=48) 51.83 (39.162) 40.00	Change from baseline (n=47) 34.80 (35.454) 29.00

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

Paediatric population

Ravulizumab SC has not been evaluated in paediatric patients.

5.2 Pharmacokinetic properties

Absorption

The estimated bioavailability of ravulizumab subcutaneous formulation is approximately 79% in adult PNH patients. Therapeutic concentrations are achieved immediately following the first dose of ravulizumab treatment.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state for ravulizumab intravenously-treated patients (i.e. patients with PNH; adult and paediatric patients with aHUS) and for ravulizumab subcutaneously-treated patients (i.e. adult patients with PNH) are presented in Table 11.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) terminal elimination half-life and clearance of ravulizumab in ravulizumab intravenously-treated patients (i.e. adult patients with PNH; adult and paediatric patients with aHUS) and for ravulizumab subcutaneously-treated patients (i.e. adult patients with PNH) are presented in Table 11.

Table 11 Distribution, biotransformation and elimination parameters following ravulizumab treatment

	Adult patients with PNH (IV)	**Adult patients with PNH (SC)**	**Adult and paediatric patients with aHUS (IV)**
Volume of distribution at steady state (litres) Mean (SD)	5.35 (0.92)	5.30 (0.95)	5.22 (1.85)
Terminal elimination half-life (days) Mean (SD)	49.7 (9.0)	52.4 (9.72)	51.8 (16.2)
Clearance (litres/day) Mean (SD)	0.08 (0.022)	0.07 (0.02)	0.08 (0.04)

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 on the PK of ravulizumab in patients with PNH and aHUS.

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

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

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 phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Polysorbate 80
Arginine
Sucrose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C)
Do not freeze.
The solution for injection in pre-filled cartridge must not be shaken or dropped.
Keep the pre-filled cartridge in the original carton in order to protect from light.
After removal from the refrigerator, Ultomiris may be stored in the original carton box at room temperature between 20°C - 25°C for up to 3 days. Do not return to the refrigerator. Discard after 3 days if unused.

6.5 Nature and contents of container

Pack size of one pre-filled cartridge and one on-body injector per carton box.

3.5 mL of sterile solution in a single-dose pre-filled cartridge (cyclic olefin polymer with elastomer septum and piston) with a resin cap. The pre-filled cartridge is assembled with a telescopic screw assembly (TSA).
The pre-filled cartridge assembly is co-packed with an on-body injector. The on-body injector is designed for use only with the provided 3.5 mL pre-filled cartridge assembly.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM Diosynth Biotechnologies U.S.A., Inc.
6051 George Watts Hill Drive
Research Triangle Park, North Carolina 27709
UNITED STATES

Patheon Biologics LLC
4766 La Guardia Drive
St. Louis, Missouri 63134
UNITED STATES

Lonza Biologics Porriño, S.L.
C/ La Relba, s/n.
Porriño
Pontevedra 36400
SPAIN

Alexion Pharma International Operations Limited
Alexion Dublin Manufacturing Facility (ADMF)
College Business and Technology Park
Blanchardstown Road North
Dublin 15, D15 R925
IRELAND

Name and address of the manufacturer(s) responsible for batch release

Alexion Pharma International Operations Limited
Alexion Dublin Manufacturing Facility (ADMF)
College Business and Technology Park
Blanchardstown Road North
Dublin 15, D15 R925
IRELAND

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth A91 P9KD
IRELAND

Almac Pharma Services Limited
22 Seagoe Industrial Estate
Craigavon, Armagh BT63 5QD
UNITED KINGDOM

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch/use of Ultomiris in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programmes, including communication media, distribution modalities, and any other aspects of the programmes, with the National Competent Authority.

The educational and controlled distribution programmes are aimed at education and instruction of healthcare professionals/patients about the detection, careful monitoring, and/or proper management of selected safety concerns associated with Ultomiris.

The MAH shall ensure that in each Member State where Ultomiris is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use Ultomiris have access to/are provided with the following educational package to be disseminated through professional bodies:
- Physician educational material
- Patient/parent information pack

The physician educational material should contain:
  - The Summary of Product Characteristics

- Guide for healthcare professionals

- **The Guide for healthcare professionals** shall contain the following key elements:
  - To address the safety concerns of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and haematological abnormalities in PNH patients, use in pregnant and breast-feeding women.
  - Treatment with ravulizumab increases the risk of *N. meningitidis* infections.
  - All patients must be monitored for signs of meningitis.
  - The need for patients to be vaccinated against *N. meningitidis* two weeks prior to receiving ravulizumab and/or to receive antibiotic prophylaxis.
  - The risk of immunogenicity and advice on post-infusion monitoring.
  - The risk of developing antibodies to ravulizumab.
  - No clinical data on exposed pregnancies is available. Ravulizumab should be given to a pregnant woman only if clearly needed. The need for effective contraception in women of childbearing potential during and up to eight months after treatment. Male patients should not father a child or donate sperm up to eight months after treatment. Breast-feeding should be discontinued during and up to eight months after treatment.
  - Risk of serious haemolysis following ravulizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
  - Risk of severe TMA complications following ravulizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only).
  - The need to explain to and ensure understanding of by patients:
    - the risk of treatment with ravulizumab (including potential risks of malignancies and haematologic abnormalities in PNH patients and serious infections)
    - the signs and symptoms of meningococcal infection and what action to take
    - the patient's/parent's guides and their contents
    - the need to carry the Patient card and to tell any healthcare practitioner that he/she is receiving treatment with ravulizumab
    - the requirement for pre-treatment vaccinations/antibiotic prophylaxis
    - the enrolment in the PNH and aHUS registries
  - Details of the PNH registry, aHUS registry and how to enter patients

The patient/parent's information pack should contain:
- Package leaflet
- A patient guide
- A parent guide
- A patient card

- **The patient guide** shall contain the following key messages:
  - To address the safety concerns of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and haematological abnormalities in PNH patients, use in pregnant and breast-feeding women.
  - Treatment with ravulizumab increases the risk of *N. meningitidis* infections.
  - Signs and symptoms of meningococcal infection and the need to obtain urgent medical care.
  - The patient alert card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with ravulizumab.
  - The importance of meningococcal vaccination prior to treatment and/or to receive antibiotic prophylaxis.
  - The risk of immunogenicity with ravulizumab, including anaphylaxis, and the need for

clinical monitoring post-infusion.
    - The need for effective contraception in women of childbearing potential during and up to eight months after treatment, and that breast-feeding should be discontinued during and up to eight months after treatment. Male patients should not father a child or donate sperm up to eight months after treatment.
    - Risk of severe haemolysis following discontinuation/postponement of ravulizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administrations (PNH only).
    - Risk of severe TMA complications following discontinuation/postponement of ravulizumab administration, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administration (aHUS only)
    - Potential risks of severe, non-neisserial infections and malignancies and haematologic abnormalities in PNH patients treated with ravulizumab.
    - Enrolment in the PNH and aHUS registries.

  The parent guide (provided together with patient guide, for intravenous formulation only) shall contain the following key messages:
    - To address the risks of meningococcal infection and serious infections in infants and children.
- **The Patient card** shall contain the following key messages:
    - Signs and symptoms of meningococcal infection
    - Warning to seek immediate medical care if above are present
    - Statement that the patient is receiving ravulizumab
    - Contact details where a healthcare professional can receive further information
    - Patient card should be retained for 8 months after last dose of ravulizumab

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense ravulizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on ravulizumab.

The MAH shall ensure that in each Member State where Ultomiris is marketed, a system aimed to control distribution of Ultomiris beyond the level of routine risk minimisation measures is in place. The following requirements need to be fulfilled before the product is dispensed:

- Submission of written confirmation of the patient`s vaccination against all available meningococcal infection serotypes *N. meningitidis* and/or prophylactic antibiotic treatment according to national vaccination guideline.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 300 mg/30 mL

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/30 mL concentrate for solution for infusion
ravulizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 30 mL contains 300 mg of ravulizumab.
(10 mg/mL)

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 5 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium chloride, polysorbate 80, and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 1 100 mg/11 mL (100 mg/mL) or Ultomiris 300 mg/3 mL (100 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 300 mg/30 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 300 mg/30 mL sterile concentrate
ravulizumab
(10 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 1 100 mg/11 mL

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 11 mL contains 1 100 mg of ravulizumab.
(100 mg/mL)

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 50 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 300 mg/30 mL (10 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 1 100 mg/11 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 1 100 mg/11 mL sterile concentrate
ravulizumab
(100 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 300 mg/3 mL

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/3 mL concentrate for solution for infusion
ravulizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 50 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 300 mg/30 mL (10 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 300 mg/3 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 300 mg/3 mL sterile concentrate.
ravulizumab
(100 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON ON-BODY DELIVERY SYSTEM

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 245 mg solution for injection in cartridge
ravulizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled cartridge of 3.5 ml contains 245 mg of ravulizumab.
(70 mg/ml)

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
This carton contains: 1 cartridge and 1 single-use on-body injector.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only.
Read the package leaflet before use.
Single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ultomiris 245 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 245 mg injection
ravulizumab
Subcutaneous use only

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ultomiris 300 mg/30 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat adult and children patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

Ultomiris is also used to treat adult patients with a certain type of disease affecting the muscles called generalised Myasthenia Gravis (gMG). In patients with gMG, their muscles can be attacked and

damaged by the immune system which can lead to profound muscle weakness, impaired vision and mobility, shortness of breath, extreme fatigue, risk for aspiration, and markedly impaired activities of daily living. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own muscles to improve muscle contraction, thereby reducing symptoms of the disease and impact of the disease on the activities of daily living. Ultomiris is specifically indicated for patients who remain symptomatic despite treatment with other therapies.

Ultomiris is also used to treat adult patients with a disease of the central nervous system that mainly affects the optic (eye) nerves and the spinal cord called Neuromyelitis Optica Spectrum Disorder (NMOSD). In patients with NMOSD, the optic nerves and spinal cord are attacked and damaged by the immune system working incorrectly, which can lead to loss of sight in one or both eyes, weakness or loss of movement in the legs or arms, painful spasms, loss of feeling, problems with bladder and bowel function and marked difficulties with activities of daily living. Ultomiris can block the body's abnormal immune response, and its ability to attack and destroy its own optic nerves and spinal cord, which reduces the risk of a relapse or attack of NMOSD.

2. What you need to know before you use Ultomiris

Do not use Ultomiris

- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions

Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms

Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain which can cause inflammation of the brain (encephalitis) and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

<u>Meningococcal infection symptoms</u>

Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive Ultomiris, you will be provided a 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis /encephalitis.
If you experience any of the following symptoms, you should immediately inform your doctor:

- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion-related reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Elderly
There are no special precautions needed for the treatment of patients aged from 65 years and over, although experience with Ultomiris in elderly patients with PNH, aHUS, or NMOSD in clinical studies is limited.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Ultomiris is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 2.65 g sodium (main component of cooking/table salt) in 720 mL at the maximal dose. This is equivalent to 133 % of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.

If you were previously receiving Ultomiris subcutaneously (given under the skin through an on-body injector), no loading dose is required. Ultomiris intravenous maintenance dose should be given 1 week after the last dose of Ultomiris subcutaneous formulation.

If you were previously receiving another medicine for PNH, aHUS, gMG, or NMOSD called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20[a]	600	600
20 to less than 30[a]	900	2,100
30 to less than 40[a]	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

[a] For patients with PNH and aHUS only.

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 2 hours.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Ultomiris".

If you stop using Ultomiris for PNH
Interrupting or ending treatment with Ultomiris may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.

The risks of stopping Ultomiris include an increase in the destruction of your red blood cells, which may cause:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),

- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for gMG
Interrupting or stopping treatment with Ultomiris may cause your gMG symptoms to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you stop using Ultomiris for NMOSD
Interrupting or stopping treatment with Ultomiris may cause NMOSD relapse to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection including meningococcal sepsis and encephalitis meningococcal.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Diarrhoea, nausea, abdominal pain
- Fever (pyrexia), feeling tired (fatigue)
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Back pain, joint pain (arthralgia)

Common (may affect up to 1 in 10 people):
- Dizziness
- Vomiting, stomach discomfort after meals (dyspepsia)
- Hives, rash, itchy skin (pruritus)
- Muscle pain (myalgia) and muscle spasms
- Influenza like illness, chills, weakness (asthenia)
- Infusion-related reaction
- Allergic reaction (hypersensitivity)
- Urinary tract infection

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)
- Gonococcal infection

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C–8°C).
Do not freeze.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 6 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 300 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium chloride, polysorbate 80, water for injections.

This medicine contains sodium (see section 2 "Ultomiris contains sodium").

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (30 mL in a vial – pack size of 1).
Ultomiris is a clear to translucent, slight whitish colour, practically free from particles solution.

Marketing Authorisation Holder
Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

Manufacturer
Alexion Pharma International Operations Limited
Alexion Dublin Manufacturing Facility
College Business and Technology Park
Blanchardstown Road North
Dublin 15, D15 R925
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris 300 mg/30 mL concentrate for solution for infusion

1- How is Ultomiris supplied?

Each vial of Ultomiris contains 300 mg of active substance in 30 mL of product solution.

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

2- Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1 100 mg/11 mL concentrates for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 5 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)	Minimum infusion duration minutes (hours)
≥ 10 to < 20[c]	600	60	60	120	113 (1.9)
≥ 20 to < 30 [c]	900	90	90	180	86 (1.5)
≥ 30 to < 40 [c]	1,200	120	120	240	77 (1.3)
≥ 40 to < 60	2,400	240	240	480	114 (1.9)
≥ 60 to < 100	2,700	270	270	540	102 (1.7)
≥ 100	3,000	300	300	600	108 (1.8)

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

Table 2: 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)	Minimum infusion duration minutes (hours)
≥ 10 to < 20[c]	600	60	60	120	113 (1.9)
≥ 20 to < 30 [c]	2,100	210	210	420	194 (3.3)
≥ 30 to < 40 [c]	2,700	270	270	540	167 (2.8)
≥ 40 to < 60	3,000	300	300	600	140 (2.3)
≥ 60 to < 100	3,300	330	330	660	120 (2.0)
≥ 100	3,600	360	360	720	132 (2.2)

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

Table 3: Supplemental dose administration reference table

Body Weight Range (kg)[a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum infusion duration minutes (hr)
⩾ 40 to < 60	600	60	60	120	30 (0.5)
	1,200	120	120	240	60 (1.0)
	1,500	150	150	300	72 (1.2)
⩾ 60 to < 100	600	60	60	120	23 (0.4)
	1,500	150	150	300	60 (1.0)
	1,800	180	180	360	65 (1.1)
⩾ 100	600	60	60	120	22 (0.4)
	1,500	150	150	300	60 (1.0)
	1,800	180	180	360	65 (1.1)

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

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- 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.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 2 hours using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2°C–8°C). Do not freeze. Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.

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

Package leaflet: Information for the user

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat adult and children patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

Ultomiris is also used to treat adult patients with a certain type of disease affecting the muscles called generalised Myasthenia Gravis (gMG). In patients with gMG, their muscles can be attacked and damaged by the immune system which can lead to profound muscle weakness, impaired vision and mobility, shortness of breath, extreme fatigue, risk for aspiration, and markedly impaired activities of daily living. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own muscles to improve muscle contraction, thereby reducing symptoms of the disease and impact of the disease on the activities of daily living. Ultomiris is specifically indicated for patients who remain symptomatic despite treatment with other therapies.

Ultomiris is also used to treat adult patients with a disease of the central nervous system that mainly affects the optic (eye) nerves and the spinal cord called Neuromyelitis Optica Spectrum Disorder (NMOSD). In patients with NMOSD, the optic nerves and spinal cord are attacked and damaged by the immune system working incorrectly, which can lead to loss of sight in one or both eyes, weakness or loss of movement in the legs or arms, painful spasms, loss of feeling, problems with bladder and bowel function and marked difficulties with activities of daily living. Ultomiris can block the body's abnormal immune response, and its ability to attack and destroy its own optic nerves and spinal cord, which reduces the risk of a relapse or attack of NMOSD.

2. What you need to know before you use Ultomiris

Do not use Ultomiris
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain which can cause inflammation of the brain (encephalitis) and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

<u>Meningococcal infection symptoms</u>

Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive Ultomiris, you will be provided a 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis/encephalitis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion-related reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Elderly
There are no special precautions needed for the treatment of patients aged from 65 years and over, although experience with Ultomiris in elderly patients with PNH, aHUS, or NMOSD in clinical studies is limited.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Ultomiris is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 0.18 g sodium (main component of cooking/table salt) in 72 mL at the maximal dose. This is equivalent to 9.1 % of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.
If you were previously receiving Ultomiris subcutaneously (given under the skin through an on-body injector), no loading dose is required. Ultomiris intravenous maintenance dose should be given 1 week after the last dose of Ultomiris subcutaneous formulation.

If you were previously receiving another medicine for PNH, aHUS, gMG, or NMOSD called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20[a]	600	600
20 to less than 30 [a]	900	2,100
30 to less than 40 [a]	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

[a] For patients with PNH and aHUS only.

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 45 minutes.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Ultomiris".

If you stop using Ultomiris for PNH
Interrupting or ending treatment with Ultomiris may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.

The risks of stopping Ultomiris include an increase in the destruction of your red blood cells, which may cause:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,

- Erectile dysfunction (impotence),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for gMG
Interrupting or stopping treatment with Ultomiris may cause your gMG symptoms to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you stop using Ultomiris for NMOSD
Interrupting or stopping treatment with Ultomiris may cause NMOSD relapse to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection including meningococcal sepsis and encephalitis meningococcal.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Diarrhoea, nausea, abdominal pain
- Fever (pyrexia), feeling tired (fatigue)
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Back pain, joint pain (arthralgia)

Common (may affect up to 1 in 10 people):
- Dizziness
- Vomiting, stomach discomfort after meals (dyspepsia)
- Hives, rash, itchy skin (pruritus)
- Muscle pain (myalgia) and muscle spasms
- Influenza like illness, chills, weakness (asthenia,)
- Infusion-related reaction
- Allergic reaction (hypersensitivity)
- Urinary tract infection

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)
- Gonococcal infection

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C–8°C).
Do not freeze.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 4 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 1 100 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, water for injections.

This medicine contains sodium (see section 2 "Ultomiris contains sodium").

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (11 mL in a vial – pack size of 1).
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris 1 100 mg/11 mL concentrate for solution for infusion

1- How is Ultomiris supplied?

Each vial of Ultomiris contains 1 100 mg of active substance in 11 mL of product solution.

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

2- Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 1 100 mg/11 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/30 mL concentrate for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 50 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)	Minimum infusion duration minutes (hours)
⩾ 10 to < 20[c]	600	6	6	12	45 (0.8)
⩾ 20 to < 30[c]	900	9	9	18	35 (0.6)
⩾ 30 to < 40[c]	1,200	12	12	24	31 (0.5)
≥ 40 to < 60	2,400	24	24	48	45 (0.8)
≥ 60 to < 100	2,700	27	27	54	35 (0.6)
≥ 100	3,000	30	30	60	25 (0.4)

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

Table 2: 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)	Minimum infusion duration minutes (hours)
⩾ 10 to < 20[c]	600	6	6	12	45 (0.8)
⩾ 20 to < 30[c]	2,100	21	21	42	75 (1.3)
⩾ 30 to < 40[c]	2,700	27	27	54	65 (1.1)
≥ 40 to < 60	3,000	30	30	60	55 (0.9)
≥ 60 to < 100	3,300	33	33	66	40 (0.7)
≥ 100	3,600	36	36	72	30 (0.5)

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

Table 3: Supplemental dose administration reference table

Body weight range (kg)[a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum infusion duration minutes (hr)
⩾ 40 to < 60	600	6	6	12	15 (0.25)
	1,200	12	12	24	25 (0.42)
	1,500	15	15	30	30 (0.5)
⩾ 60 to < 100	600	6	6	12	12 (0.20)
	1,500	15	15	30	22 (0.36)
	1,800	18	18	36	25 (0.42)
⩾ 100	600	6	6	12	10 (0.17)
	1,500	15	15	30	15 (0.25)
	1,800	18	18	36	17 (0.28)

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

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 4 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 45 min using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2°C–8°C). Do not freeze. Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.

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

Package leaflet: Information for the user

Ultomiris 300 mg/3 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat adult and children patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

Ultomiris is also used to treat adult patients with a certain type of disease affecting the muscles called generalised Myasthenia Gravis (gMG). In patients with gMG, their muscles can be attacked and damaged by the immune system which can lead to profound muscle weakness, impaired vision and mobility, shortness of breath, extreme fatigue, risk for aspiration, and markedly impaired activities of daily living. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own muscles to improve muscle contraction, thereby reducing symptoms of the disease and impact of the disease on the activities of daily living. Ultomiris is specifically indicated for patients who remain symptomatic despite treatment with other therapies.

Ultomiris is also used to treat adult patients with a disease of the central nervous system that mainly affects the optic (eye) nerves and the spinal cord called Neuromyelitis Optica Spectrum Disorder (NMOSD). In patients with NMOSD, the optic nerves and spinal cord are attacked and damaged by the immune system working incorrectly, which can lead to loss of sight in one or both eyes, weakness or loss of movement in the legs or arms, painful spasms, loss of feeling, problems with bladder and bowel function and marked difficulties with activities of daily living. Ultomiris can block the body's abnormal immune response, and its ability to attack and destroy its own optic nerves and spinal cord, which reduces the risk of a relapse or attack of NMOSD.

2. What you need to know before you use Ultomiris

Do not use Ultomiris
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain which can cause inflammation of the brain (encephalitis) and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

<u>Meningococcal infection symptoms</u>

Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive Ultomiris, you will be provided a 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis/encephalitis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms

- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion-related reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Elderly
There are no special precautions needed for the treatment of patients aged from 65 years and over, although experience with Ultomiris in elderly patients with PNH, aHUS, or NMOSD in clinical studies is limited.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Ultomiris is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 0.18 g sodium (main component of cooking/table salt) in 72 mL at the maximal dose. This is equivalent to 9.1 % of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.
If you were previously receiving Ultomiris subcutaneously (given under the skin through an on-body injector), no loading dose is required. Ultomiris intravenous maintenance dose should be given 1 week after the last dose of Ultomiris subcutaneous formulation.

If you were previously receiving another medicine for PNH, aHUS, gMG, or NMOSD called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20[a]	600	600
20 to less than 30[a]	900	2,100
30 to less than 40[a]	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

[a] For patients with PNH and aHUS only.

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 45 minutes.
If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Ultomiris".

If you stop using Ultomiris for PNH
Interrupting or ending treatment with Ultomiris may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.

The risks of stopping Ultomiris include an increase in the destruction of your red blood cells, which may cause:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),

- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for gMG
Interrupting or stopping treatment with Ultomiris may cause your gMG symptoms to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you stop using Ultomiris for NMOSD
Interrupting or stopping treatment with Ultomiris may cause NMOSD relapse to occur. Please speak to your doctor before stopping Ultomiris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection including meningococcal sepsis and encephalitis meningococcal.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Diarrhoea, nausea, abdominal pain
- Fever (pyrexia), feeling tired (fatigue)
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Back pain, joint pain (arthralgia)

Common (may affect up to 1 in 10 people):
- Dizziness
- Vomiting, , stomach discomfort after meals (dyspepsia)
- Hives, rash, itchy skin (pruritus)
- Muscle pain (myalgia) and muscle spasms
- Influenza like illness, chills, weakness (asthenia)
- Infusion-related reaction
- Allergic reaction (hypersensitivity)
- Urinary tract infection

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)
- Gonococcal infection

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C–8°C).
Do not freeze.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 4 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 300 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, water for injections.

This medicine contains sodium (see section 2 "Ultomiris contains sodium").

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (3 mL in a vial – pack size of 1).
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris 300 mg/3 mL concentrate for solution for infusion

1- How is Ultomiris supplied?

Each vial of Ultomiris contains 300 mg of active substance in 3 mL of product solution.

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

2- Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 300 mg/3 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/30 mL concentrate for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 50 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)	Minimum infusion duration minutes (hours)
⩾ 10 to < 20[c]	600	6	6	12	45 (0.8)
⩾ 20 to < 30[c]	900	9	9	18	35 (0.6)
⩾ 30 to < 40[c]	1,200	12	12	24	31 (0.5)
≥ 40 to < 60	2,400	24	24	48	45 (0.8)
≥ 60 to < 100	2,700	27	27	54	35 (0.6)
≥ 100	3,000	30	30	60	25 (0.4)

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

Table 2: 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)	Minimum infusion duration minutes (hours)
⩾ 10 to < 20[c]	600	6	6	12	45 (0.8)
⩾ 20 to < 30[c]	2,100	21	21	42	75 (1.3)
⩾ 30 to < 40[c]	2,700	27	27	54	65 (1.1)
≥ 40 to < 60	3,000	30	30	60	55 (0.9)
≥ 60 to < 100	3,300	33	33	66	40 (0.7)
≥ 100	3,600	36	36	72	30 (0.5)

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

Table 3: Supplemental dose administration reference table

Body weight range (kg)[a]	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum infusion duration minutes (hr)
⩾ 40 to < 60	600	6	6	12	15 (0.25)
	1,200	12	12	24	25 (0.42)
	1,500	15	15	30	30 (0.5)
⩾ 60 to < 100	600	6	6	12	12 (0.20)
	1,500	15	15	30	22 (0.36)
	1,800	18	18	36	25 (0.42)
⩾ 100	600	6	6	12	10 (0.17)
	1,500	15	15	30	15 (0.25)
	1,800	18	18	36	17 (0.28)

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

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 4 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 45 min using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2°C–8°C). Do not freeze. Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.

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

Package leaflet: Information for the user

Ultomiris 245 mg solution for injection in cartridge
ravulizumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.
Ultomiris should be self-administered or administered by a caregiver after training by a qualified health care professional.

What is Ultomiris used for
Ultomiris is used to treat adult patients with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months.
In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat adult patients with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ravulizumab can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

2. What you need to know before you use Ultomiris

Do not use Ultomiris
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other Neisseria infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

Meningococcal infection symptoms

Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive Ultomiris, you will or have already been provided with a 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Injection site reactions
When Ultomiris is given, you may experience reactions to the injection such as headache, lower back pain, and injection site pain.

Allergies to the adhesives of the on-body-injector

The on-body-injector of Ultomiris uses an acrylic adhesive and may cause an allergic reaction. Before starting Ultomiris, inform your doctor if you have an allergy to acrylic adhesives.
If you have an allergic reaction during the delivery of Ultomiris, remove the on-body injector and seek medical attention right away.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Ultomiris is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Ultomiris

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended maintenance dose of Ultomiris solution for injection is 490 mg administered once a week for adult patients with a body weight of 40 kg or more. See the detailed "Instructions for Use" included with this leaflet for instructions about how to store, prepare, and use your on-body delivery system.

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.

Instructions for proper use

If your doctor decides that you or a caregiver can administer your injections of Ultomiris (given under the skin through an on-body injector), you or your caregiver should receive training on the right way to prepare and inject Ultomiris.

You will need 2 on-body delivery systems (each containing 1 on-body injector and 1 pre-filled cartridge) for a full dose, and each injection will take about 10 minutes. You or your caregiver or healthcare professional can administer the injections at the same time or one after the other into your abdomen, thigh, or upper arm.

Your doctor will determine when your treatment can start as this depends on whether or not you are being treated with Ultomiris intravenously or with another medicine for PNH and aHUS called eculizumab. Table 1 shows the treatment initiation instructions to start your treatment.

Table 1: Ultomiris subcutaneous formulation treatment initiation

Population	Weight-based Ultomiris intravenous loading dose	Time of first 490 mg subcutaneous maintenance dose
Not currently on Ultomiris or eculizumab treatment	At treatment start	2 weeks after Ultomiris intravenous loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after Ultomiris intravenous loading dose
Currently treated with Ultomiris intravenous formulation	Not applicable	8 weeks after last Ultomiris intravenous maintenance dose

Detailed instructions for administration:

1. Remove two Ultomiris subcutaneous formulation cartons from the refrigerator. Two on-body injectors and two cartridges are required for a full dose.
2. Inspect the packaging. The on-body injectors or cartridges should not be used if they have been dropped or appear to be broken or damaged.
3. Wait at least 45 minutes for the on-body injectors and pre-filled cartridges in the cartons to naturally reach room temperature. Do not return to the refrigerator. Discard after 3 days at room temperature (20°C - 25°C).
4. Before administration, visually inspect the solution. The solution should not be injected if it contains flakes or particles or is cloudy or discoloured.
5. Load the first clean cartridge into the first on-body injector and secure in place before closing the cartridge door on the injector. Do not insert the cartridge more than 5 minutes before the injection to avoid drying out the solution.
6. Peel away the adhesive backing of the first on-body injector and apply the on-body injector onto the clean, dry, chosen injection site(s) (thigh, abdomen, or upper arm).
7. Start the injection by firmly pressing and releasing the blue start button.
8. Repeat for the second on-body injector.
9. Do not remove until the injection is complete (signalled by the green status light, 3 beeping sounds, and the white plunger filling the medicine window).

If you are currently not treated with Ultomiris intravenously or eculizumab
If you are currently not being treated with Ultomiris intravenously or eculizumab, your doctor will start your treatment with a loading dose of Ultomiris intravenous formulation.

If you are currently treated with eculizumab
If you are currently being treated with eculizumab, your doctor will start your treatment with an intravenous loading dose of Ultomiris on your next scheduled eculizumab dose. Two weeks after the Ultomiris intravenous loading dose, your doctor will start your treatment with Ultomiris (given via the on-body injector as injection under the skin).

If you are currently treated with Ultomiris intravenously
If you are currently being treated with Ultomiris intravenously, you will not need a loading dose of Ultomiris. Your doctor will start your treatment with Ultomiris subcutaneous formulation 8 weeks after your last Ultomiris intravenous maintenance dose.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given or have used a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget to use Ultomiris
If you missed your dosing schedule for Ultomiris you are allowed to occasionally vary by ± 1 day of the scheduled administration day. Then take the subsequent dose according to the original schedule. If you missed your dose by more than one day of the planned schedule and you are not sure when to inject Ultomiris please contact your doctor for advice and see section below "If you stop using Ultomiris".

If you stop using Ultomiris for PNH
Interrupting or ending treatment with Ultomiris may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.

The risks of stopping Ultomiris include an increase in the destruction of your red blood cells, which may cause:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection/sepsis.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):

- Headache
- Injection site reaction
- Common cold (nasopharyngitis), Upper respiratory tract infection
- Fever (pyrexia), feeling tired (fatigue)
- Diarrhoea, nausea, abdominal pain
- Joint pain (arthralgia), back pain

Common (may affect up to 1 in 10 people):
- Weakness (asthenia)
- Muscle pain (myalgia) and muscle spasms
- Vomiting, stomach discomfort after meals (dyspepsia)
- Dizziness
- Influenza like illness, chills
- Hives, Rash, itchy skin (pruritus)
- Infusion-related reaction
- Allergic reaction (hypersensitivity)

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)
- Gonococcal infection

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C–8°C).

Do not freeze.

Ultomiris may be stored in the original carton box at room temperature between 20°C - 25°C for up to 3 days. Do not return to the refrigerator. Discard after 3 days if unused.

Keep the pre-filled cartridges, and on-body injectors in the outer carton to protect from light and physical damage. Do not allow the on-body injector to get wet from water or other liquids.

Your medicine (pre-filled cartridge and on-body injector) must not be shaken or dropped.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each pre-filled cartridge contains 245 mg of ravulizumab (70 mg/mL).
- The other ingredients are: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 80, arginine, sucrose, water for injections

What Ultomiris looks like and contents of the pack
Each pack contains one pre-filled cartridge and one on-body injector.
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu