Product Monograph

Including Patient Medication Information

PrULTOMIRIS®
Ravulizumab for injection

long-acting humanized monoclonal IgG2/4K antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology

3 mL Parenteral Solution (100 mg/mL)

11 mL Parenteral Solution (100 mg/mL)

30 mL Parenteral Solution (10 mg/mL)

Pharmaceutical Standard: Professed

Complement Inhibitor

Alexion Pharma GmbH
Neuhofstrasse 34
Baar, Switzerland
6340

Date of Authorization:

2026-08-05

Imported by:
Alexion Pharma Canada Corp.
1004 Middlegate Road, Suite #5000
Mississauga, ON L4Y 1M

Control Number: 301099

Recent Major Label Changes

1 Indications, 1.1 Pediatrics	2026-06
2 Contraindications	2025-11
4.4 Administration, Home Infusion	2025-11
4.4 Dosage & Administration, 4.4 Administration	2026-01
7 Warnings and Precautions, Other Systems and Serious Infection	2026-07
7 Warnings & Precautions, 7.1.3 Pediatrics	2026-01

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes 2

Table of Contents 2

Part 1: Healthcare Professional Information 4

1. Indications 4

1.1. Pediatrics 4

1.2. Geriatrics 4

2. Contraindications 4

3. Serious Warnings and Precautions Box 5

4. Dosage and Administration 5

4.1. Dosing Considerations 5

4.2. Recommended Dose and Dosage Adjustment 5

4.2.1. Treatment Discontinuation 7

4.3. Reconstitution 7

4.4. Administration 10

4.5. Missed Dose 11

5. Overdose 11

6. Dosage Forms, Strengths, Composition, and Packaging 11

7. Warnings and Precautions 12

7.1. Special Populations 15

7.1.1. Pregnancy 15

7.1.2. Breastfeeding 15
7.1.3. Pediatrics 15
7.1.4. Geriatrics 15
8. Adverse Reactions 16
8.1. Adverse Reaction Overview 16
8.2. Clinical Trial Adverse Reactions 16
8.2.1. Clinical Trial Adverse Reactions – Pediatrics 25
8.5 Post-Market Adverse Reactions 25
9. Drug Interactions 25
9.3. Drug-Behaviour Interactions 25
9.4. Drug-Drug Interactions 25
9.5. Drug-Food Interactions 26
9.6. Drug-Herb Interactions 26
9.7. Drug-Laboratory Test Interactions 26
10. Clinical Pharmacology 26
10.1. Mechanism of Action 26
10.2. Pharmacodynamics 26
10.3. Pharmacokinetics 27
10.4. Immunogenicity 29
11. Storage, Stability, and Disposal 30
12. Special Handling Instructions 30
Part 2: Scientific Information 31
13. Pharmaceutical Information 31
14. Clinical Trials 32
16. Non-Clinical Toxicology 52
Patient Medication Information 54

Part 1: Healthcare Professional Information

1. Indications

Paroxysmal Nocturnal Hemoglobinuria (PNH)
ULTOMIRIS® (ravulizumab for injection) is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

Atypical Hemolytic Uremic Syndrome (aHUS)
ULTOMIRIS® (ravulizumab for injection) is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

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

Generalized Myasthenia Gravis (gMG)
ULTOMIRIS (ravulizumab for injection) is indicated for the treatment of adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized Myasthenia Gravis (gMG).

ULTOMIRIS was studied in adult gMG patients with a Myasthenia Gravis Foundation of America (MGFA) clinical classification Class II to IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 6.

Neuromyelitis Optica Spectrum Disorder (NMOSD)
ULTOMIRIS® (ravulizumab for injection) is indicated for the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD).

1.1. Pediatrics

- Pediatrics (1 month-18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ULTOMIRIS has only been established in pediatric patients with PNH and aHUS. . (see 7.1.3 Pediatrics)

The safety and effectiveness of Ultomiris for the treatment of gMG or NMOSD in pediatric patients below the age of 18 years has not been established.

1.2. Geriatrics

Ultomiris may be administered to 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.

2. Contraindications

Ultomiris is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6** Dosage Forms, Strengths, Composition, and Packaging.

Do not initiate Ultomiris therapy in patients:

- with unresolved *Neisseria meningitidis* infection.
- who are not currently vaccinated against Neisseria meningitidis.
- who have been vaccinated against Neisseria meningitidis for less than 2 weeks and are not on prophylactic treatment with appropriate antibiotics.

3. Serious Warnings and Precautions Box

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with Ultomiris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (See *Section 7, Warnings and Precautions*).

- **Comply with the most current National Advisory Committee on Immunization (NACI) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Patients must be vaccinated against meningococcal infections prior to, or at the time of, initiating Ultomiris, unless the risks of delaying Ultomiris therapy outweigh the risks of developing a meningococcal infection (see also *Serious Meningococcal infections* in *Section 7* for additional guidance on the management of the risk of meningococcal infections).**
- **Monitor patients for early signs of meningococcal infections and treat immediately if infection is suspected.**

Ultomiris in Canada is available under a controlled distribution program. Patients are enrolled in a dedicated Patient Support Program (PSP).

4. Dosage and Administration

4.1. Dosing Considerations

Ultomiris should be administered by a qualified healthcare professional.

Vaccinate patients according to current NACI guidelines to reduce the risk of serious infection (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions, Other Systemic and Serious Infections

Provide two weeks of antibacterial drug prophylaxis to patients if Ultomiris must be initiated immediately and vaccines are administered less than 2 weeks before starting Ultomiris therapy.

4.2. Recommended Dose and Dosage Adjustment

The recommended Ultomiris intravenous (IV) maintenance dosing in adult and pediatric patients with PNH or aHUS with a body weight greater than or equal to 5 kg or adult patients (≥ 18 years of age) with gMG or NMOSD with a body weight greater than or equal to 40 kg, is based on the patient's body weight, as shown in Table 1, with maintenance doses administered every 4 or 8 weeks, starting 2 weeks

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

For patients switching from Soliris® to Ultomiris, the loading dose of Ultomiris should be administered at the time of the next scheduled Soliris infusion, and then Ultomiris maintenance doses are administered once every 4 to 8 weeks (depending on body weight), starting 2 weeks after loading dose administration as shown in Table 1.

Table 1: Ultomiris Weight-Based Dosing Regimen

Indications	Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)	Dosing interval
PNH or aHUS	≥ 5 to < 10	600	300	Every 4 weeks
	≥ 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
PNH, aHUS, gMG or NMOSD	≥ 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

Supplemental dosing following treatment with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg)

Plasma exchange (PE), plasmapheresis (PP) and intravenous immunoglobulin (IVIg) have been shown to reduce Ultomiris serum levels. A supplemental dose of Ultomiris is required in the setting of PE, PP or IVIg Table 2).

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

Body Weight Group (kg)	Most Recent Ultomiris Dose (mg)	Supplemental Dose (mg) Following Each PP or PE Session	Supplemental Dose (mg) following Completion of IVIg Cycle
≥ 40 to ≤ 60	2,400	1,200	600
	3,000	1,500	
≥ 60 to < 100	2,700	1,500	600
	3,300	1,800	
≥ 100	3,000	1,500	600
	3,600	1,800	

Timing of Ultomiris Supplemental Dose	Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

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

Studies have not been conducted to examine the effects of hepatic impairment; however, pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment. No dose adjustment is required in patients with renal impairment. (see 10.2 Pharmacodynamics)

The clinical trials of Ultomiris in patients with aHUS included patients with other complement-mediated TMA conditions (patients with renal impairment, some of whom were receiving dialysis). No dose adjustment is required in this population. (see 10.3 Pharmacokinetics, Special Populations)

4.2.1. Treatment Discontinuation

Please refer to Section 7 WARNINGS AND PRECAUTIONS, Treatment Discontinuation for information regarding treatment discontinuation

4.3. Reconstitution

Parenteral Products: Each vial of Ultomiris is intended for single use only.

Ultomiris 100 mg/mL must be diluted to a final concentration of 50 mg/mL.
Ultomiris 10 mg/mL must be diluted to a final concentration of 5 mg/mL.
Aseptic technique must be used.

Prepare Ultomiris as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose; see **4.2** Recommended Dose and Dosage Adjustment.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 50 mg/mL for Ultomiris 100 mg/mL and 5 mg/mL for Ultomiris 10 mg/mL.
5. The prepared solution should be administered immediately following preparation. Do not administer as an intravenous push or bolus injection. Refer to the administration reference tables below for minimum infusion duration. Infusion must be administered through a 0.2 micron filter.
6. If the medicinal product is not used immediately after reconstitution, storage times at 2°C to 8°C must not exceed 24 hours taking into account the expected infusion time.

The loading, maintenance and supplemental dose administration reference tables for Ultomiris 100 mg/mL and 10 mg/mL are provided in Table 3 to Table 8 .

Table 3: Loading Dose Administration Reference Table for Ultomiris 100 mg/mL

Body Weight Range (kg)[a]	Loading Dose (mg)	Ultomiris Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 5 to < 10*	600	6	6	12	1.4	9
≥ 10 to < 20*	600	6	6	12	0.8	15
≥ 20 to < 30*	900	9	9	18	0.6	39
≥30 to < 40*	1,200	12	12	24	0.5	48
≥ 40 to < 60	2,400	24	24	48	0.8	60
≥ 60 to < 100	2,700	27	27	54	0.6	90
≥ 100	3,000	30	30	60	0.4	150

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

Table 4: Loading Dose administration Reference Table for Ultomiris 10 mg/mL

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 5 to < 10*	600	60	60	120	3.8	32
≥ 10 to < 20*	600	60	60	120	1.9	63
≥ 20 to < 30*	900	90	90	180	1.5	120
≥ 30 to < 40*	1,200	120	120	240	1.3	184
≥ 40 to < 60	2,400	240	240	480	1.9	252
≥ 60 to < 100	2,700	270	270	540	1.7	317
≥ 100	3,000	300	300	600	1.8	333

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

Table 5: Maintenance Dose Administration Reference Table for Ultomiris 100 mg/mL

Body Weight Range (kg)[a]	Maintenance Dose (mg)	Ultomiris Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 5 to < 10*	300	3	3	6	0.8	8
≥ 10 to < 20*	600	6	6	12	0.8	15
≥ 20 to < 30*	2,100	21	21	42	1.3	32
≥30 to < 40*	2,700	27	27	54	1.1	49
≥ 40 to < 60	3,000	30	30	60	0.9	67
≥ 60 to < 100	3,300	33	33	66	0.7	94
≥ 100	3,600	36	36	72	0.5	144

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

Table 6 : Maintenance Dose Administration Reference Table for Ultomiris 10 mg/mL

Body Weight Range (kg)[a]	Maintenance Dose (mg)	Ultomiris Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 5 to < 10*	300	30	30	60	1.9	31
≥ 10 to < 20*	600	60	60	120	1.9	63
≥ 20 to < 30*	2,100	210	210	420	3.3	127
≥30 to < 40*	2,700	270	270	540	2.8	192
≥ 40 to < 60	3,000	300	300	600	2.3	257
≥ 60 to < 100	3,300	330	330	660	2	330
≥ 100	3,600	360	360	720	2.2	327

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

Table 7: Supplemental Dose Reference Table for Ultomiris 100 mg/mL

Body Weight Range (kg)[a]	Supplemental Dose (mg)	Ultomiris Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 40 to < 60	600	6	6	12	0.25	48
	1,200	12	12	24	0.42	57
	1,500	15	15	30	0.5	60
≥ 60 to < 100	600	6	6	12	0.2	60
	1,500	15	15	30	0.36	83
	1,800	18	18	36	0.42	86
≥ 100	600	6	6	12	0.17	71
	1,500	15	15	30	0.25	120
	1,800	18	18	36	0.28	129

Note: Refer to Table 2 for selection of ravulizumab supplemental dose
[a]Body weight at time of treatment.
[b]Dilute Ultomiris only using 0.9% Sodium Chloride Injection, USP.

Table 8: Supplemental Dose Reference Table for Ultomiris 10 mg/mL

Body Weight Range (kg)[a]	Supplemental Dose (mg)	Ultomiris Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
≥ 40 to < 60	600	60	60	120	0.5	240

	1,200	120	120	240	1.0	240
	1,500	150	150	300	1.2	250
≥ 60 to < 100	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	328
≥ 100	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	328

Note: Refer to Table 2 for selection of ravulizumab supplemental dose
[a]Body weight at time of treatment.
[b]Dilute Ultomiris only using 0.9% Sodium Chloride Injection, USP.

Ultomiris 10 mg/mL and 100 mg/mL should not be mixed together.

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Reconstitution and dilution should only use sodium chloride 9 mg/mL (0.9%) solution for injection as diluent.

4.4. Administration

Only administer as an intravenous infusion.

Do not administer as an Intravenous Push or Bolus Injection.

- Ultomiris 100 mg/mL must be diluted to a final concentration of 50 mg/mL.
- Ultomiris 10 mg/mL must be diluted to a final concentration of 5 mg/mL.
- For intravenous infusion only.
- Must be administered through a 0.2 micron filter.

Prior to administration, the admixture should be allowed to adjust to room temperature (18°-25° C, 64°-77° F). The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

After administration of Ultomiris, flush the entire line with 0.9% Sodium Chloride Injection USP.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Home Infusion

Home infusion under the supervision of a healthcare professional may be considered for patients who are not known to be hypersensitive/allergic to ravulizumab, murine proteins, or to any ingredient in the formulation including any non-medicinal ingredient, or component of the container.

Home infusions should be performed by a qualified healthcare professional. Appropriate medical infrastructure, resources and procedures must be established and available to the healthcare professional administering home infusions.

If a patient experiences an anaphylactic reaction or another acute reaction, immediately discontinue Ultomiris infusions, initiate appropriate medical treatment and seek the attention of a physician (see 7 Warnings and Precautions).

4.5. Missed Dose

In case of a missed dose, resume the regular schedule as soon as possible. Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of Ultomiris) but the subsequent dose should be administered according to the original schedule.

5. Overdose

Ultomiris is to be administered by a healthcare professional, which minimizes the potential of a significant overdose. No cases of overdose have been reported during clinical studies.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 9: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Intravenous infusion	300 mg/ 3 mL (100 mg/mL), single dose vial 1,100 mg/11 mL (100 mg/mL), single dose vial	Polysorbate 80 Sodium phosphate, dibasic Sodium phosphate, monobasic L-arginine Sucrose Water for injection

Description

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

Ultomiris 100 mg/mL
Each vial of 3 mL contains 300 mg of ravulizumab (100 mg/mL).
Each vial of 11 mL contains 1,100 mg of ravulizumab (100 mg/mL).
Translucent, clear to yellowish colour, pH 7.4 solution.

Ultomiris 10 mg/mL
Each vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL).
Clear to translucent, slight whitish colour, pH 7.0 solution.

7. Warnings and Precautions

For serious meningococcal infections, please see 3 Serious Warnings and Precautions Box

Serious Meningococcal Infections

Due to its mechanism of action, the use of Ultomiris increases the patient's susceptibility to meningococcal infection/sepsis (Neisseria meningitidis). Meningococcal disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to, initiating Ultomiris treatment unless the risk of delaying Ultomiris treatment outweighs the risk of developing a meningococcal infection. Patients who initiate Ultomiris treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135, and B, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with Ultomiris and 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 the early signs and symptoms and advised to seek medical care immediately. Patients should be provided with information from the patient information leaflet and a patient safety card.

Other Systemic and Serious Infections

Ultomiris blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially infections caused by *Neisseria* species. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported in patients treated with Ultomiris and other terminal complement inhibitors.

In the two pivotal studies in adults patients with PNH, serious infections were reported in 17% patients including 7 fatal cases treated with Ultomiris for up to 5 years (see 8.2 Clinical Trial Adverse Reactions for PNH).

Patients should be informed of the early signs and symptoms of potential serious infections. In patients who developed an infection, the decision to continue Ultomiris treatment should be made based on the potential therapeutic benefit versus the risk of worsening infection. Physicians should advise patients about prevention of common infections and to adhere strictly to the National Advisory Committee on Immunization (NACI) vaccination recommendations.

Immunization

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease, such as hemolysis

(PNH), TMA complications (aHUS), MG exacerbation (gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

General

Sodium content

Ultomiris 10 mg/mL when diluted with 0.9% sodium chloride for IV administration contains 2.65 g sodium per 720 mL at the maximum dose, which is above Health Canada's maximum daily intake recommendation of 2.3 g sodium. This should be taken into consideration by patients on a controlled sodium diet.

Ultomiris 100 mg/mL when diluted with 0.9% sodium chloride for IV administration contains 0.18 g sodium per 72 mL at the maximum dose, which is below Health Canada's maximum daily intake recommendation of 2.3 g sodium.

Infusion Reactions

Administration of Ultomiris may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis).

In clinical trials, infusion reactions were common (1.9%). They were mild to moderate in severity and transient (e.g., skin reactions, back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity [allergic reaction], muscle spasms, dysgeusia, and drowsiness).

In case of infusion reactions, if signs of cardiovascular instability or respiratory compromise occur, administration of Ultomiris should be interrupted and appropriate supportive measures should be instituted.

Hematologic

Aplastic Anemia

In phase 3 PNH clinical studies, Ultomiris was administered to 75/222 (33.8%) patients with aplastic anemia and PNH, some of which were treated with concomitant medications for aplastic anemia (including immunosuppressive therapies). There is no evidence indicating any special precautions are required for treating patients with aplastic anemia.

Treatment Discontinuation

PNH

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

If patients with PNH discontinue treatment with Ultomiris, they should be closely monitored for signs and symptoms of hemolysis, identified by elevated lactate dehydrogenase(LDH)along with sudden decrease in – Glycophosphatidylinositol (GPI)-deficient red blood cell (RBC) clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues Ultomiris for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with Ultomiris.

aHUS
Ultomiris treatment to resolve aHUS should be a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually.

There are no specific data on Ultomiris discontinuation.

If patients must discontinue treatment with Ultomiris, they should be monitored closely for signs and symptoms of TMA for at least 12 months. However, monitoring may be insufficient to predict or prevent severe TMA complications.

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

(i) At least two of the following laboratory results observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during Ultomiris treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during Ultomiris treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during Ultomiris treatment; (results should be confirmed by a second measurement 28 days apart).

Or

(ii) any one of the following symptoms of TMA: changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure.

If TMA complications occur after Ultomiris discontinuation, consider reinitiation of Ultomiris treatment beginning with the loading dose and maintenance dose described in ***Section 4.2 Recommended Dose and Dosage Adjustment***.

gMG

Considering that gMG is a chronic disease, patients who are required to discontinue Ultomiris treatment should be monitored for symptoms of the underlying disease. If symptoms of gMG reoccur after discontinuation, consider restarting treatment with Ultomiris.

NMOSD
Use of Ultomiris in NMOSD treatment has been studied only in the setting of chronic administration and the effect of Ultomiris discontinuation has not been characterized. Patients who discontinue Ultomiris treatment should be carefully monitored for signs and symptoms of potential NMOSD relapse.

Reproductive Health Fertility

No specific non-clinical animal study on fertility has been conducted with ravulizumab (see ***16*** Non-Clinical Toxicology***, Reproductive and Developmental Toxicology***).

- **Women of childbearing potential**

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

7.1. Special Populations

7.1.1. Pregnancy

No clinical data on exposed pregnancies are available.

Non-clinical animal reproductive and developmental toxicology studies were not conducted with ravulizumab due to lack of pharmacologic activity in non-human species (see 16 Non-Clinical Toxicology).

It is unknown whether Ultomiris can cause fetal harm when administered to a pregnant woman. Human IgG are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the fetal circulation.

Ultomiris should not be used during pregnancy unless the potential benefit justifies the potential risk to the mother and the fetus.

7.1.2. Breastfeeding

It is unknown whether Ultomiris is excreted into human milk. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued during treatment and for 8 months after treatment.

7.1.3. Pediatrics

Pediatrics (1 month to <18 years of age): Use of Ultomiris in pediatric patients for treatment of PNH is supported by evidence from a pediatric clinical study (13 patients aged 9 to 17 years). The safety of Ultomiris for the treatment of PNH appears similar in pediatric and adult patients.

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

Use of Ultomiris in pediatric patients for treatment of aHUS is supported by evidence from a pediatric clinical study (18patients aged 10 months to 17 years). The safety of Ultomiris for the treatment of aHUS appears to be similar in pediatric and adult patients.

The safety and effectiveness of Ultomiris for the treatment of gMG or NMOSD in pediatric patients below the age of 18 years has not been established.

7.1.4. Geriatrics

Geriatrics (>65 years of age): Ultomiris may be administered to 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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most common adverse drug reactions reported in patients receiving ravulizumab were diarrhea, upper respiratory tract infection, pyrexia, arthralgia, back pain, fatigue, abdominal pain, urinary tract infection, dizziness, nausea, nasopharyngitis and headache. Clinically significant serious adverse reactions reported in patients in clinical trials included meningococcal infection and meningococcal sepsis.

Meningococcal infections were reported in the ravulizumab clinical development program. These patients were treated with antibiotics and recovered while remaining on ravulizumab without treatment interruption.

Patients should be informed of the signs and symptoms of serious infections including meningococcal septicemia and advised to seek medical care immediately.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

PNH

Adult patients with PNH (Primary Evaluation Period)

The data described below reflect exposure of 441 adult patients with PNH in Phase 3 studies who received Ultomiris (n = 222) or eculizumab (n = 219) at the recommended dosing regimens with median treatment duration of 6 months for Ultomiris and 6 months for eculizumab. The most frequent adverse drug reactions (>10%) with Ultomiris were upper respiratory tract infection and headache. Table 10a describes adverse reactions that occurred at a rate of 5% or more among patients treated with Ultomiris.

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

Table 10a: Treatment-Emergent Adverse Events Reported by ≥5% of Patients by Pooled Treatment Groups (Phase 3 Adult PNH Population) During Primary Evaluation Period

System Organ Class Preferred Term	All ravulizumab (N = 222)		All eculizumab (N = 219)	
	n (%)		n (%)	
Gastrointestinal disorders				
Diarrhoea	19 (8.6)		12 (5.5)	
Nausea	19 (8.6)		19 (8.7)	
Abdominal pain	13 (5.9)		16 (7.3)	
General disorders and administration site conditions				
Pyrexia	15 (6.8)		18 (8.2)	

Chest pain	5 (2.3)		14 (6.4)	
Infections and infestations				
Nasopharyngitis	32 (14.4)		38 (17.4)	
Upper respiratory tract infection	31 (14.0)		17 (7.8)	
Musculoskeletal and connective tissue				
Pain in extremity	14 (6.3)		11 (5.0)	
Arthralgia	11 (5.0)		12 (5.5)	
Myalgia	9 (4.1)		13 (5.9)	
Nervous system disorders				
Headache	71 (32.0)		57 (26.0)	
Dizziness	12 (5.4)		14 (6.4)	
Respiratory, thoracic and mediastinal				
Oropharyngeal pain	12 (5.4)		15 (6.8)	
Cough	9 (4.1)		18 (8.2)	

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
Adverse Events are coded using MedDRA 20.1.

Adult Patients with PNH following the Extension Period

Following the extension period of the two Phase 3 studies 436 adult patients with PNH were treated with Ultomiris for a median treatment duration of 3.10 (range: 0.003 - 5.61) years.

During the treatment period with ravulizumab, 96.8% of patients experienced at least 1 treatment-emergent adverse event. Serious adverse events were reported in 36% of patients and a total of 11 (2.5%) subjects died. The most frequently (≥5%) reported serious infections were upper respiratory tract infection, nasopharyngitis, COVID-19, influenza, urinary tract infection, gastroenteritis, and pneumonia. Serious infections and sepsis were reported in 17% patients including 7 fatal cases. The fatal events included one case each of sepsis, pulmonary sepsis, septic shock, Escherichia sepsis, meningococcal sepsis, COVID-19, and intracranial infection. Table 10b describes adverse reactions that occurred at a rate of 10% or more among patients treated with Ultomiris, throughout the treatment period of Ultomiris.

Table 10b: Treatment-Emergent Adverse Events Reported by ≥10% of Patients Through the Treatment Period (Phase 3 Adult PNH Population)

System Organ Class Preferred Term	**Total ravulizumab (N = 436)**
	n (%)
Gastrointestinal disorders	
Diarrhoea	73 (16.7)
Nausea	64 (14.7)
Abdominal pain	57 (13.1)
General disorders and administration site conditions	
Pyrexia	90 (20.6)
Fatigue	62 (14.2)
Infections and infestations	
Upper respiratory tract infection	113 (25.9)
Nasopharyngitis	104 (23.9)

COVID-19	58 (13.3)
Musculoskeletal and connective tissue disorders	
Arthralgia	61 (14.4)
Back pain	57 (13.1)
Nervous system disorders	
Headache	131 (30)
Dizziness	47 (10.8)
Respiratory, thoracic and mediastinal disorders	
Cough	67 (15.4)

Notes: Phase 3 PNH Population in ALXN1210-PNH-301 and ALXN1210-PNH-302.
Percentages are based on the number of Ravulizumab treated participants in the Phase 3 PNH Patient population
Adverse Events are coded using MedDRA 26.0.

Pediatric patients with PNH

In a study including 13 pediatric patients with PNH (aged 9 to 17 years), the safety profile appeared similar to that observed in adult PNH patients and in pediatric and adult aHUS patients. The most common adverse events (>20%) were upper respiratory tract infection, abdominal pain , abdominal pain ,nasopharyngitis, COVID-19, nausea and headache (see Table 11 below).

Table 11 : Adverse Reactions Reported in 10% or More of ULTOMIRIS-Treated Pediatric Patients with PNH in Study ALXN1210 PNH 304

System Organ Class Preferred Term	Treatment Naïve (N=5)	Eculizumab Experienced (N=8)	Total (N=13)
	n (%)	n (%)	n (%)
Blood and lymphatic system disorders			
Anemia[a]	1 (20)	2 (25)	3 (23)
Gastrointestinal disorders			
Abdominal pain	0 (0)	3 (38)	3 (23)
Abdominal pain upper	0 (0)	3 (38)	3 (23)
Nausea	0 (0)	3 (38)	3 (23)
Constipation	0 (0)	2 (25)	2 (15)
Diarrhea	0 (0)	2 (25)	2 (15)
General disorders and administration site conditions			
Fatigue	0 (0)	2 (25)	2 (15)
Pyrexia	1 (20)	1 (13)	2 (15)
Infections and infestations			
Upper Respiratory tract infection[b]	1 (20)	6 (75)	7 (54)
COVID-19	2 (40)	1 (13)	3 (23)
Urinary tract infection	0 (0)	2 (25)	2 (15)
Musculoskeletal and connective tissue disorders			
Pain in extremity	0 (0)	2 (25)	2 (15)
Nervous system disorders			
Headache	1 (20)	2 (25)	3 (23)

[a] Grouped term includes: anemia and iron deficiency anemia
[b] Grouped term includes: nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, viral upper respiratory tract infection, pharyngitis and rhinitis.
The data is based on final study data for ALXN1210-PNH-304 (CSR dated 2023-02-02)

aHUS

The data described below reflect exposure of 58 adult and 31 pediatric patients with aHUS in single-arm trials who received Ultomiris at the recommended dose and schedule. Table 11, Table 12 and Table 13 describe the adverse events that occurred at a rate of 10% or more among patients treated with Ultomiris in the aHUS studies. The most frequent adverse reactions reported in ≥20% of adult and pediatric patients with aHUS treated with Ultomiris were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia.

Adult patients with aHUS

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

Table 12 : Adverse Events Reported in 10% or More of Ultomiris-Treated Adult Patients with aHUS inStudy ALXN1210-aHUS-311

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

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

Grouped term includes Gastroenteritis, Gastrointestinal infection, Enterocolitis infectious, Infectious colitis, and Enterocolitis. ***: Graded per CTCAE v5.0.

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

Pediatric patients with aHUS

Table 13 : Adverse Events Reported in 10% or More of Ultomiris-Treated Pediatric Patients with aHUS in Study ALXN1210-aHUS-312

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

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

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

Table 14 : Adverse Events Reported in 10% or More of Ultomiris-Treated Patients with aHUS in Study ALXN1210-aHUS-312 by Baseline Age Group

System Organ Class Preferred Term	Age 0 to <2 (N=4)	Age 2 to <12 (N=17)	Age 12 to <16 (N=9)	Total (n=30)
	n=4 n (%)	n=17 n (%)	n=8 n (%)	n=29 n (%)
Blood and lymphatic system disorders				
Lymphadenopathy	0 (0)	2 (12)	1 (11)	3 (10)
Gastrointestinal disorders				
Diarrhea	1 (25)	4 (24)	2 (22)	7 (23)
Constipation	0 (0)	4 (24)	0 (0)	4 (13)
Vomiting	1 (25)	6 (35)	0 (0)	7 (23)
Abdominal pain	0 (0)	5 (29)	1 (11)	6 (20)
Nausea	0 (0)	3 (18)	0 (0)	3 (10)
General disorders and administration site conditions				
Pyrexia	1 (25)	7 (41)	1 (11)	9 (30)
Fatigue	1 (25)	1 (6)	1 (11)	3 (10)
Infections and infestations				
Upper respiratory tract infection*	2 (50)	11 (65)	4 (44)	17 (57)
Otitis media	1 (25)	2 (12)	0 (0)	3 (10)
Pneumonia	1 (25)	2 (12)	0 (0)	3 (10)
Gastroenteritis viral	0 (0)	2 (12)	0 (0)	2 (7)
Tonsillitis	1 (25)	2 (12)	0 (0)	3 (10)
Injury, poisoning and procedural complications				
Contusion	0 (0)	3 (18)	0 (0)	3 (10)
Investigations				
Vitamin D decreased	0 (0)	2 (12)	1 (11)	3 (10)
Metabolism and nutrition disorders				
Iron deficiency	0 (0)	3 (18)	0 (0)	3 (10)
Musculoskeletal and connective tissue disorders				
Back pain	0 (0)	2 (12)	1 (11)	3 (10)
Myalgia	1 (25)	2 (12)	0 (0)	3 (10)
Pain in extremity	0 (0)	2 (12)	1 (11)	3 (10)
Nervous system disorders				
Headache	0 (0)	5 (29)	2 (22)	7 (23)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0)	5 (29)	1 (11)	6 (20)
Nasal congestion	1 (25)	2 (12)	0 (0)	3 (10)
Skin and subcutaneous tissue disorders				
Rash	1 (25)	3 (18)	0 (0)	4 (13)
Vascular disorders				
Hypertension	2 (50)	3 (18)	2 (22)	7 (23)

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

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

gMG

Adult Patients with gMG

The data described below reflect exposure of 175 adult patients with gMG who received Ultomiris (n = 86) or placebo (n = 89) during the 26-week Randomized Controlled Period of Study ALXN1210-MG-306. The most frequent adverse reactions with Ultomiris were diarrhea (15%) and upper respiratory tract infection (12%). Table 14 describes adverse reactions that occurred at a frequency of 5% or more and at greater frequency than placebo among adult patients with gMG treated with Ultomiris. Serious adverse reactions were reported in 20 (23.3%) patients with gMG receiving Ultomiris. The most frequent serious adverse reaction reported in at least 2 (2.3%) patients treated with Ultomiris was transient ischemic attack.

Table 15 : Adverse Reactions Reported in ≥ 5% and at Greater Frequency than Placebo in Ultomiris-Treated Adult Patients with gMG in Study ALXN1210-MG-306

Body System Adverse Reaction	**Number of Patients**	
	Placebo (N=89) n (%)	**Ultomiris (N=86)** n (%)
Gastrointestinal Disorders		
Diarrhea	11 (12)	13 (15)
Abdominal pain	0	5 (6)
Infections and Infestations		
Upper respiratory tract infection*	7 (8)	10 (12)
Urinary tract infection	4 (4)	5 (6)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	5 (6)	7 (8)
Nervous System Disorders		
Dizziness	3 (3)	8 (9)

*: Grouped term includes Nasopharyngitis, Oropharyngeal pain, Pharyngitis, and Upper respiratory tract infection.

NMOSD

Adult patients with NMOSD

The safety of Ultomiris has been evaluated in 58 adult patients with NMOSD who received at least one dose of Ultomiris administered intravenously. In Study ALXN1210-NMO-307, an open-label, single-arm, multicenter trial, the most frequent adverse reactions (≥10%) with Ultomiris were diarrhoea, pyrexia, upper respiratory tract infection, nasopharyngitis, headache, back pain, urinary tract infection and arthralgia. Table 15 describes adverse reactions that occurred at a rate of 5% or more in intravenous

Ultomiris-treated patients. Serious adverse reactions were reported in 16 (27.6%) patients with NMOSD receiving Ultomiris.

Table 16 : Adverse Reactions Reported in ≥ 5% in Intravenous Ultomiris-Treated Adult Patients with NMOSD in Study ALXN1210-NMO-307

Body System Adverse Reaction	**Ultomiris (N=58)** n (%)
Blood and Lymphatic System Disorder	
Lymphadenopathy	3 (5.2)
Ear and labyrinth disorders	
Vertigo	3 (5.2)
Gastrointestinal Disorders	
Diarrhea	8 (13.8)
Nausea	5 (8.6)
Vomiting	5 (8.6)
Constipation	4 (6.9)
Gastroesophageal reflux disease	4 (6.9)
Dry mouth	3 (5.2)
General Disorders and Administration Site Reactions	
Pyrexia	6 (10.3)
Fatigue	4 (6.9)
Chills	3 (5.2)
Malaise	3 (5.2)
Vaccination site pain	3 (5.2)
Infections and Infestations	
COVID-19	28 (48.3)
Upper respiratory tract infection*	18 (31.0)
Urinary tract infection	10 (17.2)
Cystitis	5 (8.6)
Sinusitis	5 (8.6)
Oral herpes	4 (6.9)
Bronchitis	3 (5.2)
Gingivitis	3 (5.2)
Herpes zoster	3 (5.2)
Pneumonia	3 (5.2)
Injury, Poisoning and Procedural Complications	
Infusion related reaction	3 (5.2)
Limb injury	3 (5.2)
Musculoskeletal and Connective Tissue Disorders	
Back pain	8 (13.8)
Arthralgia	8 (13.8)
Pain in extremity	4 (6.9)
Muscle contracture	3 (5.2)

Myalgia	3 (5.2)
Nervous System Disorders	
Headache	19 (32.8)
Dizziness	5 (8.6)
Migraine	3 (5.2)
Psychiatric disorders	
Depression	4 (6.9)
Insomnia	4 (6.9)
Renal and urinary disorders	
Dysuria	3 (5.2)
Respiratory, thoracic and mediastinal disorders	
Cough	5 (8.6)
Skin and subcutaneous tissue disorders	
Alopecia	3 (5.2)
Pruritus	3 (5.2)
Rash	3 (5.2)
Vascular disorders	
Hypertension	3 (5.2)

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

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Please refer to Section 8.2

8.5 Post-Market Adverse Reactions

Infusion reactions

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

9. Drug Interactions

9.3. Drug-Behaviour Interactions

There are no drug-behavioural interactions known at this time.

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

4.2 Recommended Dose and Dosage Adjustment for guidance in case of concomitant PE, PP, or IVIg treatment.

Ultomiris was administered to 75/222 (33.8%) patients with a history of Aplastic Anemia and PNH some of which were treated with concomitant medications for Aplastic Anemia, including immunosuppressive therapies. No evidence of drug interactions was observed in these patients.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]), and thus preventing the generation of MAC.

In patients with PNH, complement-mediated intravascular hemolysis is blocked with ravulizumab treatment. Ravulizumab resolves complement mediated TMA in patients with aHUS.

The precise mechanism by which ravulizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

In patients with NMOSD, the exact mechanism by which ravulizumab exerts its therapeutic effect is unknown, but is presumed to involve inhibition of aquaporin-4 (AQP4) antibody induced terminal complement C5b-9 deposition and C5a-dependent inflammation.

10.2. Pharmacodynamics

Following ravulizumab treatment in both adult and pediatric complement-inhibitor naïve patients and eculizumab-experienced adult and pediatric patients with PNH, complete inhibition of serum free C5 (concentration of < 0.5 mcg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period.

Complete inhibition of serum free C5 was also observed in nearly all adult (95%) and pediatric (100%) patients with aHUS by the end of the first infusion and sustained throughout the 26-week treatment period. Complete inhibition of serum free C5 was also observed in adult patients with gMG or NMOSD by the end of the first infusion and throughout the treatment period.

The extent and duration of the pharmacodynamic response in patients with PNH and aHUS were exposure dependent for ravulizumab. Free C5 levels of <0.5 mcg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition in patients with PNH. This complete terminal complement inhibition following ravulizumab treatment led to normalization (or near normalization) of serum lactate dehydrogenase (LDH) in complement inhibitor-naïve adult PNH patients and maintenance of LDH normalization in adult PNH patients previously treated with eculizumab.

10.3. Pharmacokinetics

Ravulizumab exposure following intravenous (IV) administration increases proportionally over a dose range of 200 to 5400 mg.

Tables 15 and 16 present observed ravulizumab serum maximum concentration (Cmax) and the concentration at the end of the dosing interval (Ctrough) in PNH and aHUS patients, respectively.

Table 17 : Observed PK Parameters of ravulizumab after the loading dose and the last maintenance dose in complement inhibitor-naïve patients or prior eculizumab–treated patients with PNH

		Pediatric Patients				Adult Patients			
		ALXN1210-PNH-304				ALXN1210-PNH-301		ALXN1210-PNH-302	
PK Parameter	Dosing Period	Complement Inhibitor-Naïve		Prior eculizumab-treated		Complement Inhibitor-Naïve		Prior eculizumab-treated	
		n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)
Cmax (mcg/mL)	LD	4	733 ± 106.3 (14.5)	8	885 ± 170.8 (19.3)	125	771.4 ± 165.9 (21.5)	95	842.9 ± 203.5 (24.1)
	Last MD	4	1490 ± 397.8 (26.7)	8	1705 ± 165.4 (9.7)	124	1378.5 ± 275.9 (20.0)	95	1386.3 ± 268.4 (19.4)
Ctrough (mcg/mL)	LD	4	368 ± 54.1 (14.7)	8	452 ± 68.3 (15.1)	125	391.2 ± 136.8 (35.0)	96	405.4 ± 121.2 (29.9)
	Last MD	4	495 ± 105.4 (21.3)	8	566 ± 69.1 (12.2)	124	472.7 ± 157.9 (33.4)	95	500.8 ± 143.2 (28.6)

LD = loading dose; MD = maintenance dose

Table 18 : Observed PK Parameters of ravulizumab after the loading dose and the last maintenance dose in patients with aHUS

		Pediatric Patients (ALXN1210-aHUS-312)				Adult Patients (ALXN1210-aHUS-311)	
		< 20 kg MD Q4W		> 20 to < 40 kg MD Q8W		> 40 kg MD Q8W	
		n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)
Cmax (mcg/mL)	LD	8	656 ± 249.9 (38.1)	4	600 ± 103.8 (17.3)	52	754.3 ± 265.3 (35.2)
	MD	7	1,467 ± 554.5 (37.8)	6	1,863 ± 285.0 (15.3)	46	1,458.4 ± 256.2 (17.6)
Ctrough (mcg/mL)	LD	9	241 ± 125.6 (52.1)	5	186 ± 30.7 (16.5)	55	313.2 ± 106.2 (33.9)
	MD	7	683 ± 314.9 (46.1)	6	549 ± 187.2 (34.1)	46	506.9 ± 215.5 (42.5)

LD = Loading Dose; MD = Maintenance Dose; Q4W = Every 4 Weeks; Q8W = Every 8 Weeks

Tables 17 and 18 present observed mean pharmacokinetic parameters of ravulizumab in adult patients with gMG and NMOSD, respectively.

Table 19 : Observed PK Parameters of ravulizumab after the loading dose and the last maintenance dose in patients with gMG

		N	Adult Patients (ALXN1210-MG-306) Mean (%CV)
Cmax (mcg /mL)	LD	86	874 (184.2)
	MD	76	1548 (359.4)
Ctrough (mcg /mL)	LD	85	418 (115.5)
	MD	70	587 (173.9)

LD = Loading Dose; MD=Maintenance Dose

Table 20 : Observed PK Parameters of ravulizumab after the loading dose and the last maintenance dose in patients with NMOSD

		N	Adult Patients (ALXN1210-NMO-307) Mean ± SD (%CV)
Cmax (mcg/mL)	LD	58	935.3 ± 162.25 (17.3)
	MD	56	1836.4 ± 355.39 (19.4)
Ctrough (mcg/mL)	LD	58	459.1 ± 90.34 (19.7)
	MD	54	796.9 ± 216.04 (27.1)

LD = loading dose; MD = maintenance dose

Based on population PK modeling, the mean (%CV) AUC at steady state (AUCss) during maintenance dosing was 1,010,000 (27.2%) mcg*h/mL and 1,040,000 (24.7%) mcg*h/mL in pediatric and adult PNH patients, respectively. The mean (%CV) AUCss during maintenance dosing was 617,000 (47.4%) mcg*h/mL for pediatric aHUS patients < 20 kg dosed q4w, 1,260,000 (26.8%) mcg*h/mL for pediatric aHUS patients ≥ 20 to < 40 kg dosed q8w, and 995,000 (31.7%)mcg*h/mL for adult aHUS patients, based on population PK modeling. The mean (%CV) AUCss during maintenance dosing was 1,180,000 (28.5%) mcg*h/mL and 1,500,000 (22.9%) mcg*h/mL in adult patients with gMG and NMOSD, respectively.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state in patients with PNH, aHUS, gMG or NMOSD are shown in Table 19.

Metabolism

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.

Elimination

The mean (standard deviation [SD]) terminal elimination half-life and clearance of ravulizumab are shown in Table 21.

Table 21 : Distribution, Biotransformation, and Elimination Parameters Following Intravenous Ravulizumab Treatment based on population-PK modeling

	Adult and Pediatric Patients with PNH	Adult and Pediatric Patients with aHUS	Adult Patients with gMG	Adult Patients with NMOSD
Distribution				
Volume of distribution at steady state (liters) Mean (SD)	5.30 (0.95)	5.22 (1.85)	5.74 (1.2)	4.77 (0.819)
Biotransformation and Elimination				
Terminal elimination half-life (days) Mean (SD)	49.6 (9.08)	51.8 (16.2)	56.6 (8.4)	64.3 (11.0)
Clearance (liters/day) Mean (SD)	0.08 (0.02)	0.08 (0.04)	0.08 (0.02)	0.05 (0.016)

Special populations and conditions

No formal clinical studies of the effect of sex, race, age, hepatic or renal impairment on the pharmacokinetics of ravulizumab were conducted. Based on population PK assessment, body weight was identified as a significant covariate on the pharmacokinetics of ravulizumab. No clinically meaningful differences in pharmacokinetics of ravulizumab were observed in PNH, aHUS, gMG or NMOSD patients based on gender, age (10 months to 83 years), race, hepatic impairment, or mild to moderate renal impairment including aHUS patients with proteinuria or receiving dialysis.

No patients with severe renal impairment were enrolled in ravulizumab PNH, aHUS, gMG or NMOSD studies.

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Please refer to 7 Warnings and Precautions – Immune

As with all therapeutic proteins, there is the potential for immunogenicity with Ultomiris. Immunogenicity tests are generally product-specific and are highly dependent on the sensitivity and specificity of the assay. Comparison of incidence of antibodies between products by different tests may be misleading.
In Ultomiris studies in PNH (N = 488), aHUS (N=89), gMG (N=86) and NMOSD (N=58), treatment-emergent anti-drug antibodies were reported in 2 patients (0.28%) (one adult with PNH and one adult with aHUS). These anti-drug antibodies were transient in nature with low titer and did not correlate with clinical response or adverse events.

11. Storage, Stability, and Disposal

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

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

Do not use beyond the expiration date stamped on the carton.

12. Special Handling Instructions

Vials must not be frozen or shaken.

Ultomiris 100 mg/mL

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 to 8°C Cand up to 4 hours at room temperature.

Ultomiris 10 mg/mL

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 to 8°C and up to 6 hours at room temperature.

Refer to **4.3** Reconstitution for information on the stability and storage of diluted solutions of Ultomiris.

Part 2: Scientific Information

13. Pharmaceutical Information

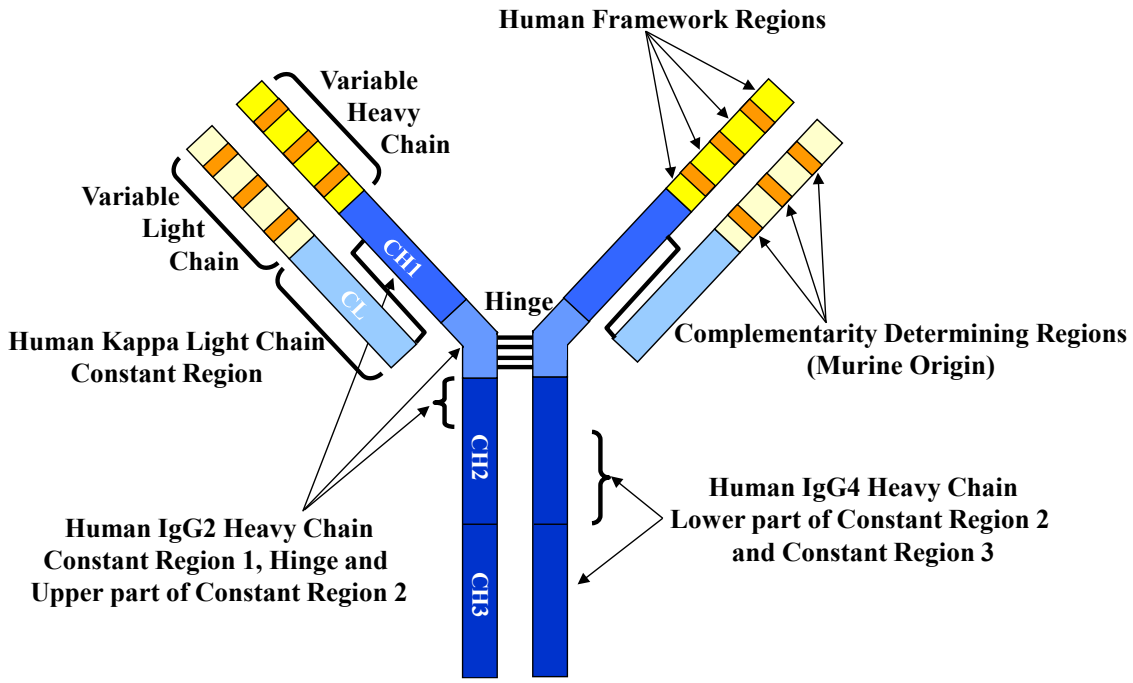
Drug Substance

Non-proprietary name of the drug substance: ravulizumab

Chemical name: Immunoglobulin G2/G4, anti-(human complement C5) (human-Mus musculus ALXN1210 heavy chain), disulfide with human-Mus musculus ALXN1210 kappa-chain, dimer

Molecular formula and molecular mass: $C_{6542}H_{10,072}N_{1704}O_{2106}S_{48}$

Structure:



Physicochemical properties: Ravulizumab drug substance is a humanized IgG2/4 kappa antibody. Table 22 lists the general physicochemical properties of ravulizumab drug substance.

Table 22: Ravulizumab Physicochemical Properties

Property	Result
Number of Amino Acids Heavy Chain[a]	448
Number of Amino Acids Light Chain[a]	226
Theoretical Molecular Weight[b]	147,827.62 Da
Isoelectric (pI) range	Multiple bands between pI 5.5 and 6.8
Extinction Coefficient at 290 nm[c]	1.479 AU$(mg/mL)^{-1}(cm)^{-1}$

[a]Antibody is comprised of duplicate identical heavy and light chains

[b]Assumes antibody contains eighteen disulfide bonds, two heavy chain N-terminal pyroglutamations, the clipping of two heavy chain C terminal lysines, and the addition of two G0F glycan residues

[c]Extinction coefficient was theoretically-determined and experimentally-confirmed

Pharmaceutical standard: Professed

Product Characteristics:

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

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

Description:

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

14. Clinical Trials

14.1 Clinical Trials by Indication

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Trial Design and Study Demographics

The safety and efficacy of Ultomiris in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302. Study ALXN1210-PNH-301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study PNH-302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

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

To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients were required to have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

A summary of key study design features and patient demographics for each study is given in Table 23 below.

Table 23 : Summary of patient demographics for clinical trials in adult and pediatric patients with PNH

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age[b] (Range)	Sex n (%)
ALXN1210 -PNH-301	Phase III, Multicentre, Open-label, randomized, active controlled in patients naïve to complement inhibitor treatment	<u>Ultomiris</u> Weight based[a]; Loading dose on day 1 followed by maintenance dose on Day 15 and every 8 weeks after; <u>Soliris</u> Induction Dose of 600 mg on Days 1, 8, 15, and 22, followed by maintenance dose of 900 mg on Day 29, and every 2 weeks after; Intravenous Infusion; 26 Weeks	<u>Ultomiris</u> n=125 <u>Soliris</u> n=121 Total n=246	<u>Ultomiris</u> 44.8 (18 – 83) <u>Soliris</u> 45 (18-86)	<u>Ultomiris</u> Male 65 (52) Female 60 (48) <u>Soliris</u> Male 69 (57) Female 52 (43)

ALXN1210-PNH-302	Phase 3, Multicentre, Open-label, randomized, active controlled in clinically stable patients treated with Soliris for at least 6 months	Ultomiris Weight based[a]; Loading dose on day 1 followed by maintenance dose on Day 15 and every 8 weeks after; Soliris 900 mg every 2 weeks Intravenous Infusion; Duration: 26 Weeks followed by an extension period in which all patients receive Ultomiris maintenance dose q8w (patients switching from eculizumab received a weight-based loading dose followed 2 weeks later by a weight-based maintenance dose q8w)	Ultomiris n=97 Soliris n=98 Total n=195	Ultomiris 46.6 (18-79) Soliris 48.8 (23-77)	Ultomiris Male 50 (51.5) Female 47 (48.5) Soliris Male 48 (49) Female 50 (51)
ALXN1210-PNH-304	Phase 3, open-label, uncontrolled, multicentre, single treatment arm study in pediatric patients with PNH who are complement inhibitor treatment-naïve or eculizumab-experienced	Ultomiris IV infusion Weight-based loading[a] dose on Day 1 and maintenance[a] dose on Day 15 and q8w (q4w for patients < 20 kg Duration 26 weeks Primary Evaluation Period Extension period up to 4 years	n=12 complement inhibitor treatment-naïve n=4 Soliris (eculizumab)-experienced n=8	14.4 (9-17)	Male 4 (33.3) Female 8 (66.7)

[a]See ***Section 4.2 Recommended Dose and Dosage Adjustment***
[b]Age (years) at first infusion in study
q4w = once every 4 weeks; q8w = once every 8 weeks

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

Study ALXN1210-PNH-301 was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry. The 26-week primary evaluation period was followed by a long-term extension period where all patients received Ultomiris. Eligible patients to enter this trial had to have a documented diagnosis of PNH with granulocyte or monocyte clone size of ≥ 5%. Ninety-eight percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy complication (3%), and other (16%).

In addition, eligible patients had to demonstrate high disease activity, defined as LDH level ≥ 1.5 × 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, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.

Patients were stratified into 6 groups based on their transfusion history in the 1 year prior to the first dose of study drug, and screening LDH levels. The patients within each of the 6 groups were then randomly assigned in a 1:1 ratio to receive either Ultomiris or Soliris. Enrollment of patients without a history of transfusion in the previous year was capped at 20%.

Table 24 presents the baseline characteristics of the PNH patients enrolled in the Complement-Inhibitor Naïve Study.

Table 24 : Baseline characteristics in the Complement-Inhibitor Naïve Study

Parameter	Statistics	Ultomiris (N = 125)	Soliris (N = 121)
Race	n (%)		
Asian		72 (57.6)	57 (47.1)
White		43 (34.4)	51 (42.1)
Black or African American		2 (1.6)	4 (3.3)
American Indian or Alaska Native		1 (0.8)	1 (0.8)
Other		4 (3.2)	4 (3.3)
Not reported		3 (2.4)	4 (3.3)
Pre-treatment LDH levels (U/L)	Median Min, max	1513.5 (378.0, 3759.5)	1445.0 (423.5, 3139.5)
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	6.0 (1, 44)	6.0 (1, 32)
Antithrombotic agents used within 28 days prior to first dose	n (%)	22 (17.6)	22 (18.2)
Patients with a history of MAVE[b]	n (%)	17 (13.6)	25 (20.7)
Patients with a history of thrombosis	n (%)	17 (13.6)	20 (16.5)
Patients with concomitant anticoagulant treatment	n (%)	23 (18.4)	28 (23.1)

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

Efficacy Results for ALXN1210-PNH-301 Study

The coprimary endpoints were transfusion avoidance, and reduction of hemolysis as directly measured

by normalization of LDH levels. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline to Day 183. Key secondary endpoints included the percent change from baseline in LDH levels; change in quality of life (FACIT-Fatigue); the proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy; and proportion of patients with stabilized hemoglobin.

Non-inferiority of Ultomiris to eculizumab was demonstrated across endpoints in the complement inhibitor naïve treatment population described in the table below.

Table 25 : Efficacy Results in the Complement-Inhibitor Naïve Study

	Ultomiris (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

Note: LDH = lactate dehydrogenase; CI = confidence interval
For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

A type I error of 1-sided 2.5% was used for the coprimary endpoints. Once noninferiority was declared for the coprimary endpoints, the key secondary endpoints were tested in a prespecified hierarchical testing procedure to control the Type-I error rate.

There was no observable difference in fatigue between Ultomiris and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

The efficacy results for the extension period included all patients treated with Ultomiris (n = 244) and had a median treatment duration of 1423 days. Only descriptive efficacy results were available, which showed that most patients appeared to maintain Ultomiris treatment responses observed during the Primary Evaluation Period (through Day 183).

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

Study PNH-302 was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with Soliris for at least the past 6 months. The 26-week primary evaluation period was followed by a long term extension period where all patients received Ultomiris.

Patients with PNH who were clinically stable (LDH level ≤1.5X ULN at screening) after having been treated with Soliris for at least 6 months were eligible for enrollment in the study. Ninety five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%).

Patients were stratified into 1 of 2 groups based on their transfusion history within the previous 12 months. Patients within each of the 2 groups were then randomly assigned in a 1:1 ratio to either continue treatment with Soliris or switch to Ultomiris.

Table 26 presents the baseline characteristics of the adult PNH patients enrolled in the Soliris-Experienced Study.

Table 26: Baseline characteristics in the Soliris-Experienced Study

Parameter	Statistics	Ultomiris (N = 97)	Soliris (N = 98)
Race	n (%)		
White		50 (51.5)	61 (62.2)
Asian		23 (23.7)	19 (19.4)
Black or African American		5 (5.2)	3 (3.1)
Other		2 (2.1)	1 (1.0)
Not reported		13 (13.4)	13 (13.3)
Unknown		3 (3.1)	1 (1.0)
Multiple		1 (1.0)	0
Pre-treatment LDH levels (U/L)	Median Min, max	224.0 135.0, 383.5	234.0 100.0, 365.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	4.0 (1, 32)	2.5 (2, 15)
Antithrombotic agents used within 28 days prior to first dose	n (%)	20 (20.6)	13 (13.3)
Patients with a history of MAVE[a]	n (%)	28 (28.9)	22 (22.4)
Patients with a history of thrombosis	n (%)	27 (27.8)	21 (21.4)
Patients with concomitant anticoagulant treatment	n (%)	22 (22.7)	16 (16.3)

[a] MAVE = major adverse vascular event

Efficacy Results for ALXN1210-PNH-302 Study

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

Non-inferiority of Ultomiris to eculizumab was demonstrated across endpoints in the patients with PNH previously treated with eculizumab described in the table below.

Table 27 : Efficacy Results in the Eculizumab-Experienced Patients with PNH Eculizumab-Experienced Study

	Ultomiris n = 97	Eculizumab n = 98	Statistic for Comparison	Treatment Effect (95% CI)
LDH Percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)
Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6 %	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin Stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

Note: CI = confidence interval. A type I error of 1-sided 2.5% was used for the primary endpoint. Once noninferiority was declared for the primary endpoint, the key secondary endpoints were tested in a prespecified sequential testing procedure to control the Type-I error rate**.**

There was no observable difference in fatigue between Ultomiris and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

The efficacy results for the extension period included all patients treated with Ultomiris (n = 192) and had a median treatment duration of 968 days. Only descriptive efficacy results were available, which showed that most patients appeared to maintain Ultomiris treatment responses observed during the Primary Evaluation Period (through Day 183).

ALXN1210-PNH-304 Study in Pediatric patients with PNH

The pediatric study (ALXN1210-PNH-304) was an open-label, single-arm study conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients with PNH. Patients who completed the 26-week primary evaluation period were followed for up to 4 years in the long-term Extension Period.

In an interim analysis a total of 12 PNH pediatric patients completed Ultomiris treatment during the Primary Evaluation Period (26 weeks). Most of the patients were between 12 and 17 years of age at first infusion, with 2 patients under 12 years old (11 and 9 years old). Based on body weight, patients received a loading dose of Ultomiris on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on Soliris therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of Soliris.

Table 28 presents the baseline characteristics of the pediatric patients with PNH enrolled in the clinical study.

Table 28: Baseline Characteristics of Pediatric Patients with PNH

Parameter	Complement Inhibitor Treatment-naïve Patients (N= 4)	Eculizumab-Experienced Patients(N=8)	All Patients N=12
Sex, n (%) Male Female	 3 (75.0) 1 (25.0)	 1 (12.5) 7 (87.5)	 4 (33.3) 8 (66.7)
Age at first infusion (years) category, n(%) Mean (SD) Median (min, max)	 14.5 (2.52) 15.0 (11, 17)	 14.4 (3.07) 15.0 (9, 17)	 14.4 (2.78) 15.0 (9, 17)
Age at first infusion (years) category, n(%) < 12 years ≥ 12 years	 1 (25.0) 3 (75.0)	 1 (25.0) 7 (87.5)	 2 (16.7) 10 (83.3)
Baseline weight (kg) category, n (%) ≥ 30 to < 40 kg ≥ 40 to < 60 kg ≥60 to < 100 kg	 1 (25.0) 2 (50.0) 1 (25.0)	 1 (12.5) 4 (50.0) 3 (37.5)	 2 (16.7) 6 (50.0) 4 (33.3)
LDH (U/L) Mean (SD) Median (min, max)	 961.38 (874.302) 565.90 (444, 2269.7)	 262.75 (106.016) 251.50 (140.5, 487)	 NA
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	2 (50.0)	2 (25.0)	4 (25.0)

Note: Percentages were based on the total number of patients in each cohort, or overall.
LDH = lactate dehydrogenase; max = maximum; min = minimum; NA = not available; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation

Efficacy Results for ALXN1210-PNH-304 Study

The weight-based dose regimen of Ultomiris provided immediate, complete, and sustained inhibition of terminal complement throughout the entire 26-week treatment period regardless of prior experience with Soliris. Following initiation of Ultomiris treatment, steady-state therapeutic serum concentrations of Ultomiris were achieved after the first dose and maintained throughout the Primary Evaluation Period in both cohorts.

Three of the 5 complement inhibitor treatment-naïve patients and 6 of the 8 Soliris-experienced patients achieved hemoglobin stabilization by Week 26, respectively. Transfusion-avoidance was reached for 10 of 12 patients during the 26-week Primary Evaluation Period. There were no breakthrough hemolysis events during the 26-week Primary Evaluation Period and no patients had post-baseline free C5 levels above 0.5 µg/mL.

A clinically relevant improvement from baseline in fatigue as assessed by Pediatric FACIT-Fatigue (i.e., mean improvement of > 3 units for Pediatric FACIT-Fatigue scores) was sustained throughout the

Primary Evaluation Period in the 5complement inhibitor treatment-naïve patients. A slight improvement was also observed in Soliris-experienced patients; however, patients were not blinded to treatment assignment. presents efficacy outcomes for the Primary Evaluation Period.

Table 29 : Efficacy Outcomes for the 26-Week Primary Evaluation Period of the Pediatric Study in Patients with PNH (ALXN1210-PNH-304)

Endpoint	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)
LDH %- Change from Baseline Mean (SD)	47.91 (52.716)	4.65 (44.702)
% of Patients achieving Transfusion Avoidance (95%CI)	14.66, 94.73)	100.0 (63.06, 100.00)
Change in FACIT-Fatigue Mean (SD)	3.40 (6.107)	1.28 (5.235)
% of patients Hemoglobin Stabilization (95%CI)	60.0 (14.66, 94.73)	75 (34.91, 96.81)
Breakthrough Hemolysis (%)	0	0[a]

[a] No patients experienced breakthrough hemolysis during the Primary Evaluation Period. One patient experienced breakthrough hemolysis after 1.8 years of treatment during the Extension Period; however, at the time of the breakthrough hemolysis event the patient had adequate C5 inhibition (free C5 < 0.5 µg/mL).

Abbreviations: CI = confidence interval, FACIT = Functional Assessment of Chronic Illness Therapy; SD = Standard Deviation

Based on these data, pediatric patients with PNH can be initiated on Ultomiris or switched from Soliris to Ultomiris. The efficacy of Ultomiris in pediatric PNH patients appears to be similar to that observed in adult PNH patients enrolled in pivotal studies.

Atypical Hemolytic Uremic Syndrome (aHUS)

Trial Design and Study Demographics

The safety and efficacy of Ultomiris in patients with aHUS was assessed in 2 open label, single arm, Phase 3 studies. Study ALXN1210-aHUS-311 enrolled adult patients and Study ALXN1210-aHUS-312 enrolled pediatric patients. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis.

A summary of key study design features and patient demographics for each study is given in Table 30 below.

Table 30: Summary of Patient Demographics for Clinical Trials in Adult and Pediatric Patients with aHUS

Study	Trial design	Dosage, route of administration	Study subjects	Mean age[b] (Range)	Sex n (%)

		and duration	(n)		
ALXN1210-aHUS-311	Phase 3, open-label, uncontrolled, multicentre, single treatment arm study in adult patients with evidence of TMA who are naïve to complement inhibitor treatment	Ravulizumab IV Weight-based loading dose on Day 1 and maintenance dose on Day 15 and q8w Duration: 26 -week initial evaluation period, up to 2-year extension period	58	42.2 (19.5-76.6)	Male 19 (33.9)
ALXN1210-aHUS-312	Phase 3, open-label, uncontrolled, multicentre, single treatment arm study in pediatric patients with evidence of TMA who are naïve to complement inhibitor treatment (Cohort 1) or were clinically stable after having been treated with eculizumab according to the labeled dosing recommendation for aHUS for at least 90 days (Cohort 2)	Ravulizumab IV Weight-based loading dose on Day 1 and maintenance dose on Day 15 and q8w (q4w for patients < 20 kg) Duration: 26 -week initial evaluation period up to 2-year extension period	31[a] Cohort 1: 21[a] Cohort 2: 10	Ravulizumab Naïve (N=18) Birth to < 2 years =2, 2 to < 6 years =9, 6 to < 12 years =5, 12 to < 18 years =2 Ravulizumab switch (N=10) Birth to < 2 years = 1, 2 to < 6 years =1, 6 to < 12 years =1, 12 to < 18 years =7	Ravulizumab-Naïve Male 8 (44.4) Ravulizumab switch Male 9 (90.0)

Loading and maintenance doses were per DOSAGE AND ADMINISTRATION, Table 1.

[a] The final study population that has received at least 1 dose of ravulizumab in Study ALXN1210-aHUS-312 is 34 patients (24 in Cohort1 and 10 in Cohort 2). The interim CSR for this study includes results through at least Week 52 (or early withdrawal) from the first 21 patients in Cohort 1 and all 10 patients in Cohort 2.

q4w = once every 4 weeks; q8w = once every 8 weeks

ALXN1210-aHUS-311 Study in Adult Patients with aHUS

The adult study was conducted in patients who were naïve to complement inhibitor treatment prior to study entry. 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 TMA were enrolled. Enrolment criteria excluded patient presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Two patients were excluded from the Full Analysis Set due to a confirmed diagnosis of Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome (STEC-HUS).

The majority of patients had extra renal signs or symptoms of aHUS at baseline. At baseline, 72.2% (n = 39) of patients had Stage 5 chronic kidney disease (CKD).

Table 31 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 31 : Baseline Characteristics in Adult Patients with aHUS

Parameter	**Statistics**	**Ravulizumab (N = 56)**
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male	 n (%)	 19 (33.9)
Race [a] Asian White Unknown Other	n (%)	 15 (26.8) 29 (51.8) 8 (14.3) 14 (7.2)
Any pretreatment extra-renal signs or symptoms of aHUS Cardiovascular Pulmonary Central nervous system Gastrointestinal Skin Skeletal muscle	n (%)	 52 (92.9) 39 (69.6) 25 (44.6) 29 (51.8) 35 (62.5) 17 (30.4) 13 (23.2)
History of transplant	n (%)	8 (14.3)
Patients postpartum	N (%)	8 (14.3)
Platelets (10^9/L) blood [normal range 130 to 400 × 10^9/L]	n Mean (SD) Median (min, max)	56 118.52 (86.440) 95.25 (18, 473)
Hemoglobin (g/L) blood [normal range 115 to 160 g/L (female), 130 to 175 g/L (male)]	n Mean (SD) Median (min, max)	56 86.26 (14.866) 85.00 (60.5, 140)
LDH (U/L) serum	n	56

[normal range 120 to 246 U/L]	Mean (SD) Median (min, max)	702.38 (557.959) 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	n (%) Mean (SD) Median (min, max)	55 15.86 (14.815) 10.00 (4, 80)
Patients on dialysis	N (%)	29 (51.8)

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

Efficacy results for ALXN1210-aHUS-311 Study

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

Other endpoints included time to Complete TMA Response, Complete TMA Response status over time, platelet count change from baseline, dialysis requirement, and renal function,

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week Initial Evaluation Period as shown in Table 32.

Table 32 : Complete TMA Response and Complete TMA Response Components Analysis for the 26-Week Initial Evaluation Period (ALXN1210- aHUS-311)

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

[a] 95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
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.

Complete TMA response was achieved at a median time of 86 days (7 to 169 days). The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months). An increase in mean platelet count was observed 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).

Renal function, as estimated glomerular filtration rate (eGFR), was improved or maintained during raviluzumab treatment. The mean eGFR (SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with Complete TMA Response, renal function continued to improve after the Complete TMA Response was achieved. Two thirds of the patient population (32/47), who were mostly CKD Stage 4 or 5 at baseline, improved by 1 or more CKD stages. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week Initial Evaluation Period. Seventeen of the 29 patients who required dialysis at study entry were able to discontinue dialysis by the end of the available follow up and 6 of 27 patients who were off dialysis at baseline were on dialysis at last available follow up.

ALXN1210-aHUS-312 Study in Pediatric Patients with aHUS

This study is a 26-week ongoing pediatric study.

A total of 18 Soliris-naïve patients with documented diagnosis of complement-mediated TMA were enrolled and included in the full analysis set. Enrolment criteria excluded patients presenting with TMA due to ADAMTS13 deficiency, STEC-HUS and genetic defect in cobalamin C metabolism. The mean age at the time of first infusion was 6.4 years. The overall mean weight at Baseline was 22 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. 3.0% (n =6) of patients had CKD Stage 5. A total of 10 patients who switched from Soliris to Ultomiris with documented diagnosis were enrolled. Patients had to have clinical response to Soliris prior to enrollment.

Table 33 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 33 : Demographics and Baseline Characteristics in Pediatric Patients with aHUS

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			
Male	n (%)	8 (44.4)	9 (90.0)
Race[a]	n (%)		
American Indian or Alaskan Native		1531	0 (0.0)
Asian		1 (5.6)	4 (40.0)
Black or African American		5 (27.8)	1 (10.0)
White		3 (16.7)	5 (50.0)
Unknown		9 (50.0)	0 (0.0)
		1 (5.6)	
Any pretreatment extra-renal signs or symptoms of aHUS	n (%)	91 7(50)	1 (10.0)
		113 (72.2)	
Cardiovascular			1 (10.0)
Pulmonary		9 (50.0)	0 (0)

Central Nervous System Gastrointestinal Skin Skeletal muscle		1 (5.6) 7 (38.9) 11 (61.1) 9 (50.0) 1 (5.6)	0 (0) 0 (0) 0 (0) 0 (0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelets (10^9/L) blood [normal range 229 to 533 × 10^9/L]	Mean (SD) Median (min, max)	60.39 (32.613) 51.25 (14, 125)	287.90 (74.596) 281.75 (207, 415.5)
Hemoglobin (g/L) blood [normal range 107 to 131 g/L]	Mean (SD) Median (min, max)	74.25 (32,106)	131.50 (11.311) 132.0 (114.5, 148)
LDH (U/L) serum [normal range 165 to 395 U/L]	Mean (SD) Median (min, max)	(772, 4985)2223.47 (1321.118)	219.40 (56.850) 206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2) [normal range ⩾ 60 mL/min/1.73 m^2]	Mean (SD) Median (min, max)	26.4 (21.17) 22.0 (10, 84)	104.90 (29.545) 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.

aHUS = atypical hemolytic uremic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum

Efficacy Results ALXN1210-aHUS-312 Study in Pediatric Patients with aHUS

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Secondary endpoints included time to Complete TMA Response, TMA response status over time, dialysis requirement, and platelet count change from baseline, dialysis requirement, and renal function. 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 34 .

Table 34 : Complete TMA Response and Complete TMA Response Components Analysis during the 26-Week Initial Evaluation Period (ALXN1210-aHUS-312)

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

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

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

Three additional patients had a Complete TMA response that was confirmed after the 26 week initial Evaluation Period.

Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (15 to 97days). The median duration of Complete TMA Response was 5.08 months (range: 3.08 to 5.54 months). An increase in mean platelet count was observed 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).

All 6 patients who required dialysis at study entry were able to discontinue dialysis; 5 of which had already done so by Day 43. The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) by 26 weeks.

Generalized Myasthenia Gravis (gMG)

Trial Design and Study Demographics

Table 35 : Summary of Patient Demographics for Clinical Trial in patients with gMG

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age[c] (Range)	Sex n (%)
ALXN1210-MG-306	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicentre study with an ongoing open-label extension Period in adult patients with gMG who were naïve to complement inhibitor treatment	Primary Evaluation Period (Day 1): Ultomiris Ravulizumab IV weight-based loading[a] dose on Day 1 and weight-based maintenance[b] dose starting on Day 15 and q8w thereafter Placebo Matched dosing to ravulizumab IV Blinded loading dose (900 mg) for all patients at Week 26 Extension Period (Week 28): Ravulizumab IV weight-based maintenance dose[b] q8w	Ultomiris n=86 Placebo n=89 Total n=175	Ultomiris 58.0 (19 to 79) Placebo 53.3 (20 to 82)	Ultomiris Male 42 (49) Female 44 (51) Placebo Male 44 (49) Female 45 (51)

[a] Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg.
[b] Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.
[c] Age at first dose of study drug (years)

The efficacy and safety of Ultomiris in adult patients with gMG was assessed in a Phase 3, randomized, double-blind, placebo-controlled, multicentre study (ALXN1210-MG-306). Patients participating in this study were randomized 1:1 to either receive Ultomiris (N=86) or placebo (N=89) for the 26-week Randomized-Controlled Period (RCP) and were subsequently allowed to enter an Open-Label Extension (OLE) Period during which all patients received Ultomiris.

Patients with gMG (diagnosed for at least 6 months) with a positive serologic test for antiacetylcholine 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 enrolled. Patients were not on chronic IVIg or PE/PP treatment within 4 weeks prior to study entry. Prior treatment with immunosuppressant therapies (ISTs) (corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus) was not required for enrollment. However, patients on ISTs were permitted to continue on therapy throughout the course of the study. In addition, rescue therapy (including high-dose corticosteroid, PE/PP, or IVIg) was allowed if a patient experienced clinical deterioration, as defined by the study protocol.

A total of 162 (92.6%) patients completed the 26-week RCP. The baseline characteristics of patients were balanced across the two treatment groups (Table 36).

Table 36 : Baseline Disease Characteristics in Study ALXN1210-MG-306

Parameter	**Statistics**	**Placebo (N = 89)**	**Ultomiris (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)
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 receiving stable corticosteroids at study entry	n (%)	65 (73.0)	56 (65.1)
Number of patients receiving other stable immunosuppressant agents* at study entry	n (%)	63 (70.8)	56 (65.1)

* Other immunosuppressant agents include 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 in the MG-ADL total score at Week 26. The MG-ADL is a patient reported 8-item categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. The MG-ADL score is composed of the following items: Assessment of the ability to speak, chew, swallow, breathe, perform self-care activities, perform physical activities, and vision-related parameters (2 items). Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with a higher score indicating more impairment.

The key secondary endpoint was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a physician-reported 13-item categorical scale that assesses the impact of muscle weakness on disease severity, based on impairments of body functions and structures. The QMG score is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is assessed on a 4-point scale where a score of 0 represents 'no weakness' and a score of 3 represents 'severe weakness' (total score 0-39).

Additionally secondary endpoints assessed at Week 26 included the proportion of patients with improvements of at least 5-points in QMG, and at least 3-points in the MG-ADL total scores, respectively, as well as changes in quality of life assessments.

Efficacy Results for ALXN1210-MG-306 Study

Ultomiris demonstrated a statistically significant change from baseline in MG-ADL total score at Week 26, as compared to placebo. The results are presented in Table 37.

Table 37 : Results of Primary and Key Secondary Efficacy Endpoint

Change from baseline to Week 26	**Placebo (N = 89) LS Mean (SEM)**	**Ultomiris (N = 86) LS Mean (SEM)**	**Treatment Effect (95% CI)[a]**
MG-ADL	-1.4 (0.37)	-3.1 (0.38)	-1.6 (-2.6, -0.7)[b]
QMG	-0.8 (0.45)	-2.8 (0.46)	-2.0 (-3.2, -0.8)[b]

[a] Based on a mixed effect repeated measures analysis

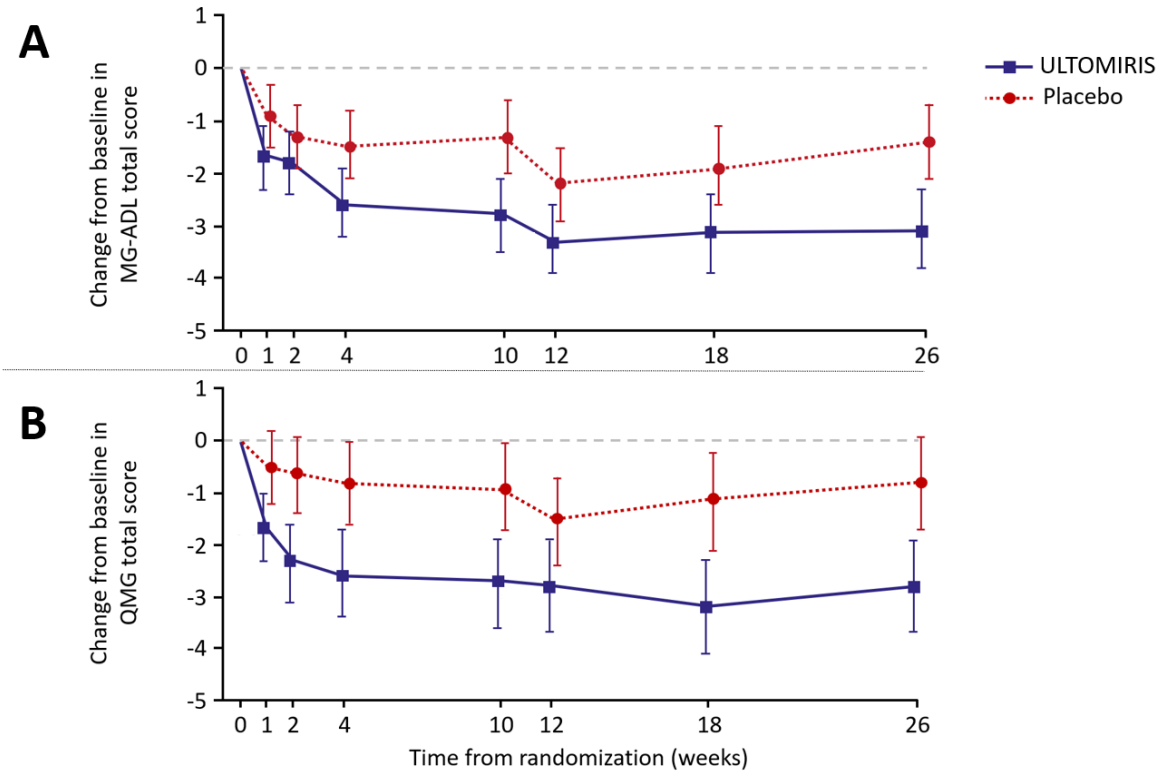
[b] Statistically significant under multiplicity control for Ultomiris vs placebo comparison ($p < 0.05$).

Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; SEM = standard error of mean

The proportion of clinical responders was consistently greater for Ultomiris compared to placebo for QMG ≥ 5-point improvement [30.0% vs. 11.3%; risk ratio (95% confidence interval [CI]): 2.7 (1.4, 5.3)] and MG-ADL ≥ 3-point improvement [56.7% vs. 34.1%; risk ratio (95% CI): 1.6 (1.2, 2.3)] endpoints.

In patients treated with Ultomiris, favourable changes were observed in all domain scores of the MG-ADL and in the ocular, bulbar, and limb domain scores of the QMG.

Figure 1: Change from Baseline in MG-ADL Total Score (A) and QMG Total Score (B) Through Week 26 of the Randomized Controlled Period of ALXN1210-MG-306 (Mean and 95% CI)[a]



Note: Loading dose at Week 0 followed by maintenance doses at Week 2 and then Q8W thereafter.
[a]Based on a mixed effect repeated measures analysis

In the ongoing uncontrolled Open Label Extension of ALXN-MG-306, among the subset of subjects randomized to ravulizumab, the mean changes in MG-ADL and QMG observed at Week 52 were -4.2 (n=35) and -4.7 (n=34)

Neuromyelitis Spectrum Disorder (NMOSD)

Trial Design and Study Demographics

ALXN1210-NMO-307 Study in Adult Patients with NMOSD

The efficacy and safety of Ultomiris in adult patients with anti-AQP4 antibody-positive NMOSD was assessed in Study ALXN1210-NMO-307, which was designed as an open-label, multicenter study using the placebo arm of the Study ECU-NMO-301 (eculizumab versus placebo in patients with NMOSD) to demonstrate Ultomiris superiority over placebo. Patients participating in Study ALXN1210-NMO-307 received Ultomiris intravenously in the Primary Treatment Period that ended when the last enrolled patient completed (or discontinued prior to) 52 weeks on study, representing a median study duration of 73.5 weeks (minimum 13.7, maximum 117.7 weeks). Patients were subsequently allowed to enter a Long-Term Extension Period during which all patients continued to receive Ultomiris for up to 2 years.

A summary of key study design features and patient demographics for each study is given in Table 38 below.

Table 38: Summary of Patient Demographics for Clinical Trials in Adult Patients with NMOSD

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age[c] (Range)	Sex n (%)
ALXN1210-NMO-307	Phase III, External Placebo-Controlled, Open-Label, Multicentre Study to evaluate the efficacy and safety of Ravulizumab in adult patients with NMOSD	Ravulizumab IV weight-based loading[a] dose on Day 1 and weight-based maintenance[b] dose starting on Day 15 and q8w thereafter Duration: Median study duration of 73.5 weeks (minimum 13.7, maximum 117.7 weeks)	Ultomiris n=58 Placebo n=47	Ultomiris 46.0 (18, 74) Placebo 44.0 (21, 75)	Ultomiris Female 52 (89.7 %) Placebo 42 (89.4 %)

[a] Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg.
[b] Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.
[c] Age at first dose of study drug (years)

Study ALXN1210-NMO-307 enrolled 58 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 ≤ 7. Prior treatment with immunosuppressant therapies (ISTs) was not required for enrollment. However, patients on selected ISTs (ie, corticosteroids, azathioprine, mycophenolate mofetil, tacrolimus) were permitted to continue on therapy, with a requirement for stable dosing until they reached Week 106 in the study. At that point, changes could be made at the discretion of the Investigator. 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.

A total of 56 (96.6%) patients completed the Primary Treatment Period of Study ALXN1210-NMO-307. 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 42.5 years, ranging from 16 to 73 years. Baseline characteristics for Study ALXN1210-NMO-307 and for the comparative external placebo arm of study ECU-NMO-301 are shown in Table 39 below.

Table 39 : Baseline characteristics of the adult patients enrolled in Study ALXN1210-NMO-307 and comparative external placebo arm of study ECU-NMO-301.

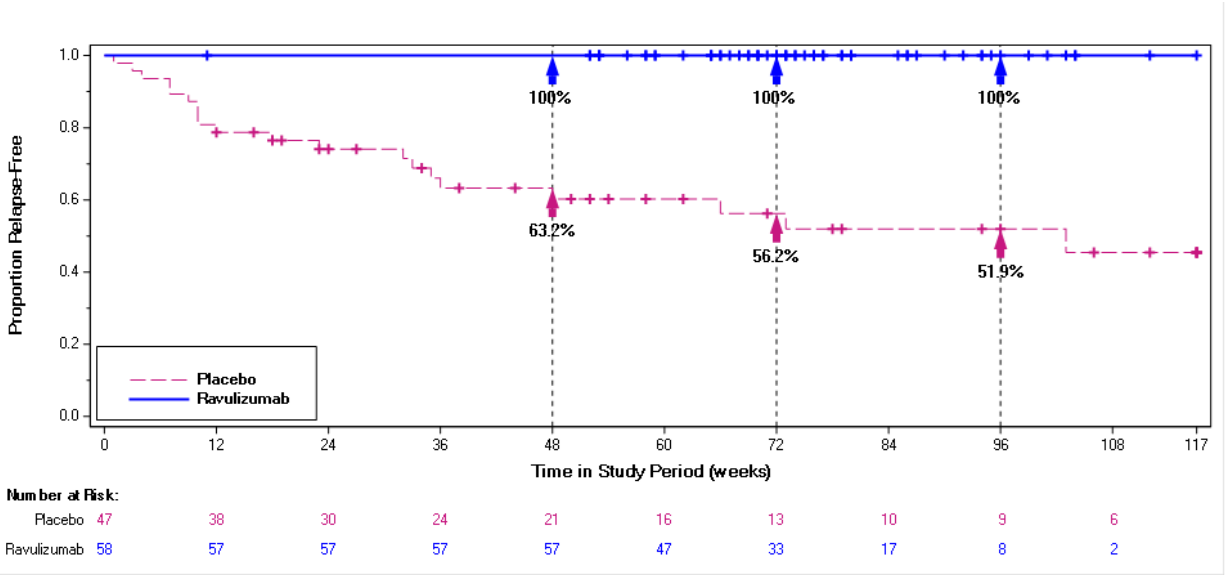
Variable	Statistic	ECU-NMO-301 Placebo (N=47)	ALXN1210-NMO-307 Ultomiris (N=58)
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Mean (SD)	6.60 (6.59)	5.19 (6.38)
	Median	3.76	1.96
	Min, max	0.51, 29.10	0.19, 24.49
Historical ARR within 24 months prior to Screening	Mean (SD)	2.07 (1.04)	1.87 (1.59)
	Median	1.92	1.44
	Min, max	1.0, 6.4	0.5, 6.9
Baseline HAI score	Mean (SD)	2.1 (1.40)	1.2 (1.42)
	Median	2.0	1.0
	Min, max	0, 6	0, 7
Baseline EDSS score	Mean (SD)	4.26 (1.51)	3.30 (1.58)
	Median	4.00	3.25
	Min, max	1.0, 6.5	0.0, 7.0
Historical rituximab use	n (%)	20 (42.6)	21 (36.2)
Number of patients receiving stable corticosteroids only at study entry	n (%)	11 (23.4)	11 (19)
Number of patients not receiving any IST at study entry	n (%)	13 (27.7)	31 (53.4)

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

Efficacy Results for ALXN1210-NMO-307 study

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 Ultomiris-treated patients during the median Primary Treatment Period of 73.5 weeks reflecting 84.01 patient years. The observed proportion of adjudicated on-trial relapse was 42.6 in the external placebo arm. The proportion of relapse-free patients at Week 48 was 100 % on Ultomiris versus 63.2% in the external historical placebo arm. All Ultomiris-treated patients remained relapse free at Week 72, including patients not on concomitant treatment.

Figure 2: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-Trial Relapse in Study ALXN1210-NMO-307 and Comparative Placebo Arm of STUDY ECU-NMO-301.



Ultomiris-treated patients had an adjudicated on-trial annualized relapse rate (ARR) of zero as compared to 0.25, which was chosen to represent a conservative ARR that may be experienced in the NMOSD patient population. This corresponds to comparing zero case of relapse on Ultomiris-treated patients with 21 expected relapses on untreated patients over the same study period.

In the final efficacy analysis, with a median follow-up of 170.29 weeks (range: 13.7 to 243.0 weeks; 189.7 patient-years), no adjudicated on-trial relapses were observed in patients treated with Ultomiris through the end of the study. Treatment with Ultomiris was associated with a low adjudicated on-trial annualized relapse rate (ARR). At the end of the study, including additional follow-up from the long-term extension period, the ARR (95% CI) was 0.00 (upper bound 0.019). Lower rates of relapse-related hospitalizations and use of acute relapse therapies (including corticosteroids and plasma exchange) were observed in Ultomiris-treated patients compared with placebo. In addition, among patients receiving concomitant immunosuppressive therapy at baseline, some were able to reduce or discontinue at least one therapy during treatment with Ultomiris.

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

16. Non-Clinical Toxicology

Animal toxicology studies have not been conducted with ravulizumab due to a lack of pharmacologic activity in non-human species, but were conducted in mice with a surrogate murine anti-mouse C5 antibody, BB5.1.

General toxicology:

A 26-week repeat-dose toxicity study in mice was performed with the surrogate antibody BB5.1. Animals were intravenously administered vehicle control or BB5.1 at a dose of 30 mg/kg body weight

once or twice weekly. C5-induced hemolytic activity in an ex vivo assay was effectively blocked throughout the course of the study in both female and male mice. Administration with BB5.1 did not affect any of the toxicity parameters examined. The no-observed-adverse-effect level (NOAEL) in this study was 30 mg/kg body weight administered twice weekly.

Genotoxicity:

No studies have been performed to evaluate the genotoxic potential of ravulizumab.

Carcinogenicity:

No studies have been performed to evaluate the carcinogenic potential of ravulizumab.

Reproductive and developmental toxicology:

Three reproductive and developmental studies were conducted with the murine surrogate molecule, BB5.1.

In a fertility and early embryonic development study, BB5.1 was administered by intravenous injection to male and female mice from prior to mating, throughout mating, and post-mating until termination (males) or through early gestation until gestation day (GD) 7 (females) at a dose of 30 mg/kg body weight once or twice weekly. This study included assessment of potential effects on general toxicity, estrous cycling, sperm parameters, mating behavior, implantation, general fertility, and litter parameters. There were no test article-related adverse findings in this study. Thus, the NOAEL for effects on fertility and early embryonic development was 30 mg/kg body weight administered twice weekly.

In an embryo-fetal development study, the maternal and embryo/fetal toxicity and teratogenic potential of BB5.1 were evaluated following administration to pregnant mice during the period of organogenesis (GD 6 to 15). BB5.1 was administered by intravenous injection at a dose of 30 mg/kg body weight once or twice weekly. Fetal malformations consisted of two cases of retinal dysplasia and one case of umbilical hernia observed among 230 fetuses from dams administered BB5.1 twice weekly. Similar findings were not observed following administration of BB5.1 once weekly. No other adverse findings were observed following administration of BB5.1, including no increase in fetal loss or neonatal death. Based on the fetal soft tissue malformations observed following twice weekly dosing, the NOAEL for developmental toxicity was 30 mg/kg body weight administered once weekly.

A pre- and postnatal development study was conducted to evaluate the effects of BB5.1 on pregnant and lactating female mice and the development of the offspring. BB5.1 was administered to female mice by intravenous injection at a dose of 30 mg/kg body weight once or twice weekly from implantation through weaning (GD 6 to lactation day 18). No adverse effects on pregnancy or delivery were observed following administration of BB5.1. However, a higher number of male offspring from dams administered BB5.1 became moribund or died (1/25 in the control group, 2/25 in the 30 mg/kg body weight once weekly group, and 5/25 in the 30 mg/kg body weight twice weekly group). There was also an increased incidence of dilated renal pelves in male offspring of both BB5.1 dose groups. No other adverse developmental findings were observed in surviving offspring, including in reproductive performance.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ULTOMIRIS®
[Ravulizumab for injection]

This Patient Medication Information is written for the person who will be taking **ULTOMIRIS®.** This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.
This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ULTOMIRIS®,** talk to a healthcare professional.

Serious warnings and precautions box

- Ultomiris increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.
- You must be vaccinated against meningococcal infections prior to, or at the time of, initiating Ultomiris.
- You must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics.

Consult your doctor before you take Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* prior to, or at the time of, beginning therapy. If you start therapy less than 2 weeks after being vaccinated, you must take antibiotics to reduce the risk of infection for 2 weeks. Ensure that your current meningococcal vaccinations are up to date. You should also be aware that vaccination may not 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 be provided a card to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis. This card is named: “Patient Safety Card”.

If you experience any of the following symptoms, you should immediately inform your doctor:

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

What ULTOMIRIS is used for:

Paroxysmal Nocturnal Hemoglobinuria
Ultomiris is used for the treatment of adult and pediatric patients one month of age and older with a certain type of disease affecting the blood system called Paroxysmal Nocturnal Hemoglobinuria (PNH).

In patients with PNH, their red blood cells can be destroyed which can lead to low blood counts (anemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

atypical Hemolytic Uremic Syndrome
Ultomiris is used for the treatment of adult and pediatric patients one month of age and older with atypical Hemolytic Uremic Syndrome (aHUS).

In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning.

Generalized Myasthenia Gravis
Ultomiris is used to treat adult patients with a certain type of disease affecting the muscles called generalized Myasthenia Gravis (gMG).

In patients with gMG, their muscles can be damaged by their immune system, which can cause severe muscle weakness, impaired vision and mobility, shortness of breath, extreme fatigue, risk for aspiration (i.e. choking caused by inhaling food or liquid), and decreased ability to perform activities of daily living.

Neuromyelitis Optica Spectrum Disorder
Ultomiris is used to treat adult patients with a disease of the central nervous system that mainly affects the eye nerves and the spinal cord called neuromyelitis optica spectrum disorder (NMOSD).

In patients with NMOSD, the eye nerves and spinal cord are attacked and damaged by the immune system.

How ULTOMIRIS works:

Ultomiris contains the active substance ravulizumab and that belongs to a class of medicines called monoclonal antibodies. Ravulizumab attaches to and stops the action of a specific protein in the body preventing one very specific component of your immune system from attacking and destroying vulnerable and needed blood, tissue and muscle cells.

In patients with NMOSD, the eye nerves and spinal cord are attacked and damaged by the immune system. Ultomiris is presumed to block a specific area of the body's inflammatory response, and its ability to attack and destroy its own eye nerves and spinal cord.

The ingredients in ULTOMIRIS are:

Medicinal ingredients: Ravulizumab

100 mg/mL
Non-medicinal ingredients: L-arginine, polysorbate 80 (vegetable origin), sodium phosphate dibasic, sodium phosphate monobasic, sucrose, water for injection.

10 mg/mL
Non-medicinal ingredients: Polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, water for injection.

ULTOMIRIS comes in the following dosage forms:

100 mg/mL
Single use vial of 300 mg concentrate for solution for infusion; 3 mL
Single use vial of 1,100 mg concentrate for solution for infusion; 11 mL

10 mg/mL
Single use vial of 300 mg concentrate for solution for infusion; 30 mL

Do not use ULTOMIRIS if:

- you have not received a meningococcal vaccine before or at the time of starting therapy

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ULTOMIRIS. Talk about any health conditions or problems you may have, including if you:

- have an infection (including if you have or are at risk for gonorrhea infection)
- have any other unresolved infections

Other warnings you should know about:

Allergic Reactions
Ultomiris contains a protein than may cause allergic reactions in some people. Tell your doctor or nurse right away if you get any of these symptoms during your Ultomiris infusion:

- chest pain
- trouble breathing or shortness of breath
- swelling of your face, tongue, or throat
- feel faint or pass out

Infusion reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) such as headache, lower back pain, and infusion-related pain. Some patients may experience infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness). Tell your doctor or nurse right away if you develop these symptoms, or any other symptoms during your Ultomiris infusion.

Pregnancy and Nursing
Ultomiris should not be used during pregnancy unless the potential benefit justifies the potential risk to the mother and the fetus.
The use of effective contraception during treatment and up to 8 months after treatment should be considered in women who are able to get pregnant.

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 contains sodium
Ultomiris 10 mg/mL when diluted with 0.9% sodium chloride for IV administration contains 2.65 g sodium per 720 mL at the maximum dose, which is above Health Canada's maximum daily intake recommendation of 2.3 g sodium. This should be taken into consideration by patients on a controlled sodium diet.

Ultomiris 100 mg/mL when diluted with 0.9% sodium chloride for IV administration contains 0.18 g sodium per 72 mL at the maximum dose, which is below Health Canada's maximum daily intake recommendation of 2.3 g sodium.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ULTOMIRIS:

The treatment will be given by your doctor or other health care provider by infusing a dilution of the Ultomiris vial from a drip bag through a tube directly into one of your veins. It is recommended that the beginning of your treatments, called the loading phase, will extend over 2 weeks, followed by a maintenance phase. The doses administered are based on your body weight, as shown in Table 1, your doctor will calculate this. Two weeks after receiving your loading dose, you will be administered Ultomiris once every 8 weeks.
If you were receiving Soliris prior to receiving Ultomiris, the loading dose should be administered 2 weeks after the last Soliris infusion. The infusion will take approximately 2 hours.

Pediatric patients:

Pediatric patients who weigh ≥ 40 kg are treated with the adult dosing recommendations. The weight-based dosing recommendation and dosing interval for pediatric patients below < 40 kg are shown in Table 1 with maintenance doses starting 2 weeks after loading dose administration.

Table 1: Ultomiris Weight-Based Dosing Regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)	Dosing interval
≥ 5 to < 10	600	300	Every 4 weeks
≥ 10 to < 20	600	600	Every 4 weeks
≥ 20 to < 30	900	2,100	Every 8 weeks
≥ 30 to < 40	1,200	2,700	Every 8 weeks
≥ 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

Administration of PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) or intravenous immunoglobulin (IVIg) may reduce Ultomiris serum levels.

Overdose:

If you think you, or a person you are caring for, have taken too much [BRAND NAME], contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

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:

- a significant fall in your red blood cell counts (anemia),
- 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).

aHUS

If you have aHUS, your doctor will need to monitor you closely for at least 12 months after stopping treatment for signs of worsening aHUS or problems related to a type of abnormal clotting and breakdown of your red blood cells called thrombotic microangiopathy (TMA). Symptoms or problems that can happen with TMA may include:

- confusion or loss of consciousness
- seizures
- chest pain (angina)
- difficulty breathing
- blood clots or stroke

gMG

Interrupting or stopping treatment with Ultomiris may cause your gMG symptoms to reoccur or become worse. Talk to your doctor about the management of your gMG before stopping Ultomiris.

They will discuss with you the possible side effects and risks of interrupting or stopping treatment with Ultomiris.

NMOSD

Interrupting or ending treatment for Ultomiris may cause your NMOSD symptoms to reoccur or become worse. Talk to your doctor about the management of your NMOSD before stopping Ultomiris. They will discuss with you the possible side effects and risks of interrupting or stopping treatment with Ultomiris.

Symptoms of NMOSD may include:

- 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

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.

Possible side effects from using ULTOMIRIS:

These are not all the possible side effects you may have when taking ULTOMIRIS. If you experience any side effects not listed here, tell your healthcare professional.

The most serious side effect is meningococcal infection/sepsis.

If you experience any of the meningococcal infection symptoms, you should immediately inform your doctor. Symptoms are listed under the 'Serious Warnings & Precautions' Box and in your Patient Safety Card.

The most common side effects in adult patients with PNH treated with Ultomiris are upper respiratory infection and headache.

The most common side effects of Ultomiris in pediatric patients with PNH are abdominal pain and common cold.

The most common side effects of Ultomiris in patients with aHUS are upper respiratory tract infection, common cold and headache.

The most common side effects of Ultomiris in people with gMG are diarrhea and upper respiratory tract infection.

The most common side effects of Ultomiris in adult patients with NMOSD are headache, back pain, arthralgia, urinary tract infection, common cold, sinus infection, fever, diarrhea, feeling sick (nausea).,

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Common cold (nasopharyngitis)	x		
Diarrhea	x		
Fatigue	x		
Headache	x		
Nausea	x		
Upper respiratory tract infection	x		
COMMON Abdominal pain	x		
Back Pain	x		
Dizziness	x		
Fatigue	x		
Fever		x	
Hives	x		
Influenza-like illness		x	
Itchiness	x		
Joint Pain	x		
Muscle Pain	x		
Muscle Spasm	x		
Nausea	x		
Rash	x		
Upset stomach	x		
Vomiting	x		
Weakness	x		
UNCOMMON Anaphylactic reaction[a]		x	x
Chills		x	
Gonococcal infection[b]		x	
Hypersensitivity[c]		x	
Meningococcal infection		x	x
Meningococcal sepsis		x	x

[a] Estimated from postmarketing experience

[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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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 to 8°C).
Do not freeze. Do not shake.
Keep out of reach and sight of children.

Store in the original package in order to protect from light.

If you want more information about ULTOMIRIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.alexion.com; or by calling 1-888-765-4747.

This leaflet was prepared by Alexion Pharma GmbH.

Date of Authorization: 2026-08-05