swissmedic

Date: 13 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Ultomiris

International non-proprietary name: ravulizumab
Pharmaceutical form: concentrate for a solution for infusion
Dosage strength(s): 1100 mg/11 mL, 300 mg/3 mL, 300 mg/30 mL
Route(s) of administration: intravenous
Marketing authorisation holder: Alexion Pharma GmbH
Marketing authorisation no.: 67278
Decision and decision date: approved on 29 August 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
aHUS	Atypical haemolytic uraemic syndrome
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AQP4	Aquaporin-4
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
gMG	Generalised myasthenia gravis
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IST	Immunosuppressive therapy
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
LTEP	Long-term extension period
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NMOSD	Neuromyelitis optica spectrum disorder
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PE	Plasma exchange
PIP	Paediatric investigation plan (EMA)
PNH	Paroxysmal nocturnal haemoglobinuria
PP	Plasmapheresis
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 1 of the TPA.
Orphan drug status was granted on 27 February 2023.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	19 October 2022
Formal control completed	3 November 2022
List of Questions (LoQ)	2 March 2023
Response to LoQ	11 April 2023
Preliminary decision	19 June 2023
Response to preliminary decision	10 July 2023
Final decision	29 August 2023
Decision	approval

3 Medical context

Neuromyelitis optica (NMO, Devic's disease) is a rare, complement-mediated autoimmune inflammatory disease of the central nervous system (CNS). After the discovery of antibodies against aquaporin 4 (AQP4-IgG), the term NMO spectrum disorder (NMOSD) was introduced to acknowledge a more diverse clinical presentation. It is characterised by demyelination and axonal damage, which predominantly affect the optic nerves and spinal cord (longitudinally extensive transverse myelitis). Whether it is a variant of multiple sclerosis (MS) or a separate disease entity has long been discussed. Nowadays, it is recognised as a discrete disease. In contrast to diseases such as multiple sclerosis, patients with NMOSD do not typically recover from their relapse-related neurologic deficits (also known as "attacks") and the disease generally progresses in a stepwise fashion to neurologic disability. Therefore, relapse prevention is the primary goal of NMOSD therapeutics. Together with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), MS and NMOSD are summarised as autoimmune CNS demyelinating disorders, which share similarities but also display differences in clinical characteristics and pathogenesis.

The incidence of NMOSD in Europe ranges from 0.053 to 0.4 per 100,000 individuals, with prevalence rates from 0.72 to 4.4 per 100,000.

Treatment of NMOSD is comprised of both acute treatment of relapses and long-term relapse prevention therapy. In Switzerland, 2 treatment options have been approved so far for long-term treatment for adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive: satralizumab (Enspryng®) and eculizumab (Soliris®).

4 Nonclinical aspects

The applicant requested a new indication for Ultomiris for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive. The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.

Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

Sparse pharmacokinetic (PK) and pharmacodynamic (PD) data in patients with NMOSD following the administration of ravulizumab were collected in the Phase 3 study ALXN1210-NMO-307. 58 adult complement inhibitor treatment-naïve patients were included in the PK/PD set.

Following the loading dose as well as the maintenance doses, all trough concentrations were above the target therapeutic PK threshold of 175 µg/mL.

Based on previously developed population PK models for healthy subjects and patients with paroxysmal nocturnal haemoglobinuria (PNH) as well as for patients with generalised myasthenia gravis (gMG), a population PK analysis was conducted to identify factors that account for variability of the ravulizumab PK in patients with NMOSD. The PK of ravulizumab was well described by a 2-compartment model with first-order elimination and estimated allometric exponents for body weight on central/intercompartmental clearance (CL/Q) and central/peripheral compartment volume of distribution (Vc/Vp). Body mass index on Vc was identified as a statistically significant covariate and was included in the population PK model. Only the effect of plasmapheresis (PP) / plasma exchange (PE) on central clearance was included in the model, since limited data on IVIg intervention were available. Similar exposures between patients with NMOSD and gMG were observed.

Two patients received rescue therapy followed by supplemental dosing with ravulizumab. One patient received 5 PE/PP interventions and 1 patient received 1 IVIg intervention. In both cases, ravulizumab concentrations above the PK therapeutic target threshold as well as complete terminal complement inhibition were maintained.

Immediate and complete terminal complement inhibition (defined as serum free C5 concentrations <0.5 µg/mL) was observed in study ALXN1210-NMO-307.

5.2 Dose finding and dose recommendation

No separate dose finding for adult patients with NMOSD has been conducted. The ravulizumab treatment regimen is body weight-based and identical to the approved dosing for adult patients with PNH, atypical haemolytic uraemic syndrome (aHUS), or gMG. It includes a loading dose followed by maintenance doses administered every 8 weeks, starting 2 weeks after the loading dose.

5.3 Efficacy

The proposed indication for Ultomiris® (ravulizumab) was supported by data from one Phase 3 clinical study ALXN1210-NMO-307 (study 307). It is an ongoing, external placebo-controlled, open-label, multicentre clinical study to evaluate the efficacy, safety, PK, PD, and immunogenicity of ravulizumab in adult patients with NMOSD who are AQP-4 antibody-positive.

Study 307 employs a single-arm treatment design, utilising the placebo group from the eculizumab NMOSD clinical development programme of study ECU-NMO-301 (study 301, conducted 2014 to 2018) as an external placebo control.

All clinical analyses presented were based on a database lock date of 25 April 2022.

A total of 58 patients were enrolled and treated with ravulizumab in study 307. As of the database lock date, n=56 (96.6%) had completed the primary treatment period. Two patients discontinued due to adverse events. All 47 patients randomised to placebo in study 301 were eligible and were included in the full analysis set (FAS).

Most patients in both the ravulizumab (n = 50; 86.2%) and placebo (n = 45; 95.7%) groups had used immunosuppressive therapy (IST) for NMOSD relapse prevention prior to study treatment. A greater percentage of patients in the placebo group were on ISTs at baseline compared with the ravulizumab

group (72.3% and 48.3%, respectively). Patients on ISTs at baseline were required to remain on a stable dose of IST within predefined limits. Changes in IST during the study were not allowed.

Study 307 met its primary endpoint ("Time to first adjudicated on-trial relapse and relapse risk reduction", p<0.0001) and objective to demonstrate the efficacy of ravulizumab for the treatment of adult patients with NMOSD. No adjudicated on-trial relapses were observed in patients treated with ravulizumab during the primary treatment period of 73.5 median weeks of duration, compared with 20 patients (42.6%) in the placebo group from study 301.

A consistent treatment effect was observed for ravulizumab compared with placebo across all pre-specified subgroups (i.e. age, gender, race, geographic region); however, some subgroups included a small number of patients, which limits interpretation of these results.

In the requested updated analysis (data cutoff date 15 July 2022), no adjudicated on-trial relapse was documented during 90.93 median weeks of treatment with ravulizumab.

Due to imbalances mainly in the disease characteristics at baseline between patients in the ravulizumab group of study 307 and patients in the external placebo control of study 301, a direct comparison of the magnitude of the treatment effect in the primary efficacy analysis is hampered. Patients in the ravulizumab group of study 307 tended to be less clinically affected than those in the external placebo group of study 301 at baseline (time from initial clinical presentation of NMOSD, historical annualised relapse rate (ARR), Hauser Ambulation Index (HAI), Expanded Disability Status Scale (EDSS), no IST). These baseline imbalances might potentially have favoured ravulizumab, which should be considered in the interpretation of the treatment effect.

Further secondary efficacy analyses, e.g. clinically important worsening in EDSS score from baseline, were mostly not statistically significant.

Of note, ravulizumab has not been studied for the *acute* treatment of relapses in NMOSD patients.

5.4 Safety

As of the database lock date, n=56 (96.6%) patients had completed the primary treatment period (PTP) of study 307. Two patients were reported to have discontinued treatment due to adverse events. Median (minimum, maximum) study duration was 73.50 (13.7, 117.7) weeks. 55 (94.8%) ravulizumab-treated patients were followed for > 12 months, with 21 (36.2%) patients followed for > 18 months. Treatment compliance (defined as receiving the full intended amount of the study drug) was 100% in all 58 patients treated with ravulizumab.

Overall, treatment-emergent adverse events (TEAEs) were reported in 53 (91.4%) patients in the ravulizumab group. Most TEAEs were not related to the study drug and were mild in severity. Treatment-emergent serious adverse events (TESAEs) were reported in 8 (13.8%) patients in the ravulizumab group. Two (3.4%) patients in the ravulizumab group experienced an event of meningococcal infection. Both patients were promptly treated and recovered with no sequelae; however, for one of these patients, this led to withdrawal of the study drug.

No deaths were reported.

The most common TEAEs (occurring in ≥ 10% of patients) included COVID-19 (14 [24.1%] patients), headache (14 [24.1%] patients), back pain (7 [12.1%] patients), arthralgia (6 [10.3%] patients), and urinary tract infection (6 [10.3%] patients). It should be noted that study 307 was initiated on 13 December 2019, and approximately 90% of patients were enrolled during the COVID-19 pandemic (i.e. March 2020 or later).

Other serious adverse events (SAEs) included five cases of infections (encephalitis, meningococcal infection, intervertebral discitis, meningococcal sepsis, and pneumonia), one case of spinal osteoarthritis, one case of invasive lobular breast carcinoma, and one case of suicidal ideation.

No clinically significant trends were observed in any laboratory parameters or in any vital sign parameters over time. No pregnancies were reported during the study.

Five (8.6%) of the 58 patients in the ravulizumab-treated group exhibited pre-existing immunoreactivity. No treatment-emergent ADA responses were observed in patients treated with

ravulizumab. No impact was observed on ravulizumab pharmacokinetics, pharmacodynamics, safety, or efficacy in those patients with NMOSD treated with ravulizumab. None of the samples that were positive in the ADA assay exhibited neutralising activity in the neutralising antibody assay.

Withdrawal, rebound effect, and potential for drug abuse were not specifically investigated in the clinical studies of ravulizumab.

Cumulatively as of the requested update (cutoff date 15 July 2022), 383 TEAEs were reported in 54 (93.1%) patients in the ravulizumab group, including 52 events reported for 27 patients during the LTEP. The most common TEAEs remained consistent. Cumulatively, no deaths were reported. Cumulatively, 2 (3.4%) patients experienced suicidal ideation during treatment with ravulizumab. During the PTP, one patient with a history of suicidal ideation experienced a TESAE of suicidal ideation during treatment with ravulizumab. Potential infusion reactions were reported for 4 patients during the LTEP who had not experienced infusion reactions during the PTP. None were serious or required interruption or withdrawal of ravulizumab. Overall, no new safety signals were observed during the LTEP as of the cutoff date.

Overall, the safety profile of ravulizumab in patients with NMOSD was consistent with that shown for other already approved indications.

Due to its identical binding epitope on C5 and mechanism of action of near-complete terminal complement inhibition, ravulizumab carries the same severe risk of meningococcal disease as eculizumab. Accordingly, identical risk mitigation measures apply.

Overall, the safety database is limited, both in terms of exposed patients and long-term exposure. No data are available for women who are pregnant as well as patients < 18 years of age.

5.5 Final clinical benefit-risk assessment

Overall, the benefit-risk balance of ravulizumab is favourable for the treatment of adult patients with NMOSD who are AQP4 antibody-positive.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Ultomiris was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ULTOMIRIS® 300 MG/30 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

ULTOMIRIS® 300 MG/3 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

ULTOMIRIS® 1100 MG/11 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

Composition

Active substances

Ravulizumab, produced from genetically modified ovarian cells from the Chinese hamster.

Excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate heptahydrate
Ultomiris 300 mg/3 mL and 1100 mg/11 mL: L-arginine
Ultomiris 300 mg/3 mL and 1100 mg/11 mL: sucrose
Ultomiris 300 mg/30 mL: sodium chloride
Ultomiris 300 mg/30 mL: 115 mg sodium per 30 mL vial
Ultomiris 300 mg/3 mL: 4.6 mg sodium per 3 mL vial
Ultomiris 1100 mg/11 mL: 16.8 mg sodium per 11 mL vial
Polysorbate 80
Water for injection

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
Ultomiris 300 mg/30 mL:
Clear to translucent solution, slight whitish colour, pH 7.0.
One 30 mL vial contains 300 mg of ravulizumab (10 mg/mL) and 115 mg of sodium.
After dilution, the final concentration of the solution to be infused is 5 mg/mL.
Ultomiris 300 mg/3 mL:
Translucent, clear to yellowish solution, pH 7.4.
One 3 mL vial contains 300 mg of ravulizumab (100 mg/mL) and 4.6 mg of sodium.
After dilution, the final concentration of the solution to be infused is 50 mg/mL.
Ultomiris 1100 mg/11 mL:
Translucent, clear to yellowish solution, pH 7.4.

One 11 mL vial contains 1100 mg of ravulizumab (100 mg/mL) and 16.8 mg of sodium.
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Indications/Uses

Paroxysmal nocturnal haemoglobinuria (PNH)

Ultomiris is used in the treatment of adult and paediatric patients with a body weight of 10 kg or above with PNH:

- in patients with haemolysis with one or more clinical symptom(s) indicative of high disease activity,
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section "Properties/Effects").

Atypical haemolytic uraemic syndrome (aHUS)

Ultomiris is used in the treatment of patients weighing 10 kg and over with aHUS who have not previously been treated with complement inhibitors (complement inhibitor-naïve patients) or have received eculizumab for at least 3 months, with evidence of a response to eculizumab.

Generalised myasthenia gravis (gMG)

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

Neuromyelitis optica spectrum disorder (NMOSD)

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

Dosage/Administration

Ravulizumab must be administered by healthcare professionals and under the supervision of a physician experienced in the treatment of patients with haematological, renal, neuromuscular or neuroinflammatory disorders.
Before initiating treatment it should be ensured that active meningococcal infection/sepsis is not present and that the patient has been adequately vaccinated against meningococcal disease according to the official vaccination recommendations (see “Contraindications” and “Warnings and precautions”).
In order to improve the traceability of bio-technological medicinal products, recording of the name and the batch number of each treatment is recommended.

Adult patients with PNH, aHUS, gMG or NMOSD

The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. In adult patients (≥ 18 years of age), the maintenance doses should be administered at 8-week intervals, starting 2 weeks after administration of the loading dose. The dosing regimen may occasionally vary by ± 7 days from the scheduled infusion day (except for the first maintenance dose of ravulizumab) but the subsequent dose should be administered according to the original schedule.

For patients being switched from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion. Maintenance doses are then administered once every 8 weeks, starting 2 weeks after administration of the loading dose, as shown in Table 1.

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

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

*The first maintenance dose is administered 2 weeks after the loading dose.

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

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

Table 2: Supplemental dose of ravulizumab after PP, PE, or IVIg

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

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

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

In aHUS, ravulizumab treatment to resolve thrombotic microangiopathy (TMA) manifestations should be for a minimum duration of 6 months. After that, the duration of treatment should be decided individually for each patient. In patients who have a higher risk of recurrence of TMA, in the treating doctor's opinion (or according to the clinical indication), long-term treatment may be necessary (see section "Warnings and precautions").

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

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

Patients with impaired hepatic function

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

Patients with impaired renal function

No dose adjustment is required for patients with renal impairment (see section "Pharmacokinetics").

Elderly patients

No dose adjustment is required for patients with PNH, aHUS, gMG or NMOSD aged 65 years and over. There is no evidence indicating that special precautions are required for treating geriatric patients. There is, however, only limited experience with ravulizumab in in elderly patients with PNH, aHUS or NMOSD.

Children and adolescents

Children and adolescents with PNH and aHUS weighing ≥ 40 kg are treated according to the dosage recommendations for adults (Table 1). Table 3 shows the doses and dose intervals calculated by body weight for children and adolescents weighing ≥ 10 kg to < 40 kg.
In patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion. Maintenance doses should then be administered according to a dosing regimen based on body weight, as shown in Table 3, starting 2 weeks after administration of the loading dose.

Table 3: Weight-based ravulizumab dosage regimen in children and adolescents with PNH or aHUS weighing less than 40 kg

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

*The first maintenance dose is administered 2 weeks after the loading dose.

There is only limited evidence of the safety and efficacy of ravulizumab in patients weighing under 10 kg. The currently available data are described in section “Undesirable effects”, but no dosage recommendations can be given for patients weighing under 10 kg.

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

Ravulizumab has not been studied in children and adolescents with gMG or NMOSD.

Mode of administration

For intravenous infusion only.
This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.
Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1100 mg/11 mL concentrate for solution for infusion.

Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion
Ultomiris concentrate for solution for infusion is presented in 3 mL and 11 mL vials (100 mg/mL) and must be diluted to a final concentration of 50 mg/mL. Following dilution, Ultomiris is to be administered as an intravenous infusion using a syringe pump or infusion pump over a minimum period of 10 to 75 minutes (0.17 to 1.3 hours), depending on body weight (see Tables 4 and 5 below).

Table 4: Infusion rate for doses of Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion

Body weight (kg)[a]	Loading dose (mg)	Minimum infusion time Minutes (hours)	Maintenance dose (mg)	Minimum infusion time Minutes (hours)
≥ 10 to < 20[b]	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30 [b]	900	35 (0.6)	2100	75 (1.3)
≥ 30 to < 40 [b]	1200	31 (0.5)	2700	65 (1.1)
≥ 40 to < 60	2400	45 (0.8)	3000	55 (0.9)
≥ 60 to < 100	2700	35 (0.6)	3300	40 (0.7)
≥ 100	3000	25 (0.4)	3600	30 (0.5)

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

Table 5: Dose administration rate for supplemental doses of Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

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

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

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Ultomiris concentrate for solution for infusion is presented in 30 mL vials (10 mg/mL) and must be diluted to a final concentration of 5 mg/mL. Following dilution, Ultomiris is to be administered by intravenous infusion with a syringe pump or infusion pump over a minimum period of 22 to 194 minutes (0.4 to 3.3 hours), depending on body weight (see Tables 6 and 7 below).

Table 6: Infusion rate for doses of Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight[a] (kg)	Loading dose (mg)	Minimum duration of infusion Minutes (hours)	Maintenance dose (mg)	Minimum duration of infusion Minutes (hours)
≥ 10 to < 20[b]	600	113 (1.9)	600	113 (1.9)
≥ 20 to < 30[b]	900	86 (1.5)	2,100	194 (3.3)
≥ 30 to < 40[b]	1,200	77 (1.3)	2,700	167 (2.8)
≥ 40 to < 60	2,400	114 (1.9)	3,000	140 (2.3)
≥ 60 to < 100	2,700	102 (1.7)	3,300	120 (2.0)
≥ 100	3,000	108 (1.8)	3,600	132 (2.2)

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

Table 7: Infusion rate for supplemental doses of Ultomiris 300 mg/30 mL concentrate for solution for infusion

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

[a] Body weight at time of treatment.

[b] Refer to Table 2 for selection of ravulizumab supplemental dose

For instructions on dilution of the medicinal product before administration, see section "Instructions for handling".

Contraindications

- Hypersensitivity to the active substance or to any of the substances listed in the section "Excipients".
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation (see section "Warnings and precautions").
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section "Warnings and precautions").
- Patients with hereditary complement deficiencies (see “Warnings and precautions”).

Warnings and precautions

Serious meningococcal infection

Due to its mechanism of action, ravulizumab increases the patient's susceptibility to meningococcal infection/sepsis *(Neisseria meningitidis)*. Meningococcal disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to starting treatment with ravulizumab. Patients who start ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135 and B, where available, are recommended for prevention of the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to the official guidelines for vaccination use. If the patient is being switched from eculizumab treatment, physicians should verify that there is adequate protection against meningococcal disease according to the official guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. Attention should be paid to official guidance on the appropriate use of antibiotics. Cases of serious meningococcal infections/sepsis have been reported in patients treated with ravulizumab. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with other terminal complement inhibitors. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and seek immediate medical care. Physicians should provide patients with the patient information brochure and patient safety card.

Immunisation

It is recommended that before the start of treatment with ravulizumab, patients start their vaccinations according to the current vaccination guidelines.

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

Patients aged under 18 years must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, with rigorous adherence to the national vaccination recommendations for each age group.

Other systemic infections

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

Patients should be informed about potential serious infections and their symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion reactions

Administration of ravulizumab may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials, infusion reactions were common (1.6%). These reactions were mild to moderate in severity and transient, including lower back pain, abdominal pain, muscle cramps, drop in blood pressure, rise in blood pressure, muscle rigidity, limb symptoms, drug sensitivity (allergic reaction), dysgeusia (altered sense of taste) and drowsiness. In cases of infusion reaction and signs of cardiovascular instability or respiratory compromise, the infusion of ravulizumab should be interrupted and appropriate supportive measures should be taken.

Discontinuation of treatment in PNH

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

Discontinuation of treatment in aHUS

No specific data on the cessation of ravulizumab are available. In a long-term, prospective observational study, discontinuation of treatment with the complement C5 inhibitor (eculizumab) led to a 13.5 times higher rate of TMA recurrence, and there was a tendency towards a decline in kidney function compared with patients who continued the treatment.

If patients need to discontinue treatment with ravulizumab, they should be continuously and closely monitored for signs and symptoms of TMA. However, it is possible that monitoring is not sufficient for predicting or preventing serious TMA complications.

Complications of TMA after cessation of treatment can be identified by any of the following observations:

(i) At least two of the following laboratory findings are simultaneously present: a decrease of at least 25% in the platelet count from either the baseline count or the highest platelet count during ravulizumab treatment; increase of at least 25% in serum creatinine from the baseline value or from the lowest value during ravulizumab treatment; or increase of at least 25% in serum LDH from the baseline value or from the lowest value during ravulizumab treatment (the results should be confirmed by a second measurement) or

(ii) any of the following symptoms of TMA: change in mental state or seizures or other extrarenal manifestations of TMA, including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea or thrombosis.

If complications of TMA occur after cessation of ravulizumab, resumption of ravulizumab treatment with the loading and maintenance doses should be considered (see section “Dosage/Administration”).

Treatment discontinuation for gMG

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

Switch from eculizumab to ravulizumab

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

Discontinuation of treatment in NMOSD

Ravulizumab for the treatment of NMOSD has only been studied in the context of long-term use and the effect of discontinuing ravulizumab has not been described. Patients in whom Ultomiris treatment has been discontinued should be closely monitored for signs of a possible relapse of the NMOSD.

Patients with Shiga toxin-producing *E. coli* haemolytic uraemic syndrome (STEC-HUS)

No data are available on the use of Ultomiris in patients with STEC-HUS.

Sodium content

Ultomiris 300 mg/30 mL concentrate for solution for infusion

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

Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion

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

Interactions

No interaction studies have been performed.

Based on the potential inhibitory effect of ravulizumab on the complement-dependent cytotoxicity of rituximab, ravulizumab may reduce the expected pharmacodynamic effects of rituximab.

See Section “Dosage/Administration” for guidance in case of concomitant PE, PP, or IVIg treatment.

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

Pregnancy, lactation

Pregnancy

Women of child-bearing potential

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

Pregnancy

No clinical data available on use in pregnant patients.

Nonclinical reproductive toxicology studies were not conducted with ravulizumab (see section "Preclinical data"). Reproductive toxicology studies which assessed the effect of C5 blockade on the reproductive system were conducted in mice using the murine surrogate molecule BB5.1. No specific test article-related reproductive toxicities were identified in these studies. Human IgG is known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the foetal circulation. Insufficient data are available from animal studies with respect to reproductive toxicity (see section "Preclinical data").

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

Lactation

It is unknown whether ravulizumab is excreted into human milk. Nonclinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to the young resulting from consuming milk from treated dams.

A risk to infants cannot be excluded.

Since many medicinal products and immunoglobulins are excreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment with ravulizumab and up to 8 months after treatment.

Fertility

No specific non-clinical studies on fertility have been conducted with ravulizumab.
Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on the fertility of the treated females or males.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (with the frequency statement “very common”) are diarrhoea, upper respiratory tract infection, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infections and meningococcal sepsis (see section "Warnings and precautions").

Tabulated list of adverse reactions

Table 8 gives the adverse reactions observed in clinical trials and during post marketing surveillance. Adverse reactions are listed by MedDRA system organ class and frequency using the MedDRA convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (frequency cannot be estimated from available data).

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

Table 8: Adverse reactions from clinical trials and post marketing

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon ((≥ 1/1000, < 1/100)
Infections and infestations	Upper respiratory tract infection, nasopharyngitis	Urinary tract infection	Meningococcal infection [c], gonococcal infection [d]
Immune system disorders			Anaphylactic reaction [a], hypersensitivity [b]
Nervous system disorders	Headache	Dizziness	
Gastrointestinal disorders	Diarrhoea	Vomiting, abdominal pain, nausea, dyspepsia	
Skin and subcutaneous tissue disorders		Urticaria, pruritus, rash	
Musculoskeletal and connective tissue disorders		Arthralgia, back pain, myalgia, muscle spasms	
General disorders and administration site conditions		Pyrexia, influenza-like illness, chills, asthenia, fatigue	
Injury, poisoning and procedural complications		Infusion-related reaction	

[a] Estimated from post-marketing experience
[b] Hypersensitivity is a Preferred Term (PT) group term: drug hypersensitivity with related causality and Preferred Term hypersensitivity
[c] Meningococcal infection includes the following Preferred Terms (PT): meningococcal infection, meningococcal sepsis and meningococcal encephalitis
[d] Gonococcal infection includes disseminated gonococcal infection

Description of selected undesirable effects

Meningococcal infection/sepsis

Vaccination reduces but does not completely eliminate the risk of meningococcal infections. In clinical trials, < 1% of patients developed serious meningococcal infections while receiving treatment with ravulizumab. All of these were adults with PNH or NMOSD and had been vaccinated. Please refer to the section "Warnings and precautions" for information on prevention and treatment of suspected meningococcal infection. Meningococcal infections in patients treated with ravulizumab presented as meningococcal sepsis and encephalitis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised that they must seek immediate medical care.

Immunogenicity

Treatment with any therapeutic protein may induce an immune response. In adult PNH patient studies (N = 261), in a study in children and adolescents with PNH (N = 13), in aHUS studies (N = 89), in a gMG study (N = 86) and in an NMOSD study (N = 58) only two cases (0.40%) of development of treatment-related anti-drug antibodies have been reported with ravulizumab (1 adult patient with PNH

and 1 adult patient with aHUS). These anti-drug antibodies were transient in nature with a low titre and did not correlate with clinical response or adverse events.

Children and adolescents

Paroxysmal nocturnal haemoglobinuria (PNH)

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

Atypical haemolytic uremic syndrome (aHUS)

In children and adolescents with signs of aHUS (aged 10 months to under 18 years) who took part in the study ALXN1210-aHUS-312, the safety profile of ravulizumab seemed similar to that in adult patients with signs of aHUS. The safety profiles in the different paediatric age groups seem to be similar. The safety data for patients aged under 2 years are limited to four patients. The most commonly reported adverse effect in paediatric patients was fever (32.3%).

Generalised myasthenia gravis (gMG)

Ravulizumab has not been studied in children and adolescents with gMG.

Neuromyelitis optica spectrum disorder (NMOSD)

Ravulizumab has not been studied in children and adolescents with NMOSD.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Patients who experience overdose should have their infusion interrupted immediately and be closely monitored.

Properties/Effects

ATC-Code

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

Mechanism of action

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

Pharmacodynamics

Following ravulizumab treatment in adult and paediatric patients with PNH not previously treated with complement inhibitors and patients with PNH previously treated with eculizumab in Phase 3 trials, immediate, complete and sustained inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all patients. Immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS, in adult patients with gMG and in adult patients with NMOSD by the end of the first infusion and throughout the 26-week treatment period.
The extent and duration of the pharmacodynamic response in patients with PNH, aHUS, gMG or NMOSD were exposure-dependent with ravulizumab. Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition. In gMG, terminal complement activation leads to MAC deposition at the neuromuscular junction and impairment of neuromuscular transmission. In NMOSD, uncontrolled terminal complement activation caused by anti-AQP4 autoantibodies leads to MAC- and C5a-dependent inflammation, which results in astrocyte necrosis, increased permeability of the blood-brain barrier and damage to surrounding glial cells and neurons.

Clinical efficacy

Paroxysmal nocturnal haemoglobinuria
The safety and efficacy of ravulizumab in adult patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:

- a trial in adult patients with PNH who had not previously received complement inhibitor treatment,
- a trial in adult patients with PNH who were clinically stable after having been treated with eculizumab for at least the previous 6 months.

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

Patients were vaccinated against meningococcal infection prior to or at the start of treatment with ravulizumab or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.
There were no noteworthy differences in demographics or in characteristics present at start of the trial between the ravulizumab and eculizumab treatment groups in either of the Phase 3 trials. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 trials.

Trial in adult patients with PNH who had not previously received complement inhibitor treatment
The trial of patients not previously treated with complement inhibitors was a 26-week multicentre open-label randomised active-controlled Phase 3 trial, conducted in 246 patients who had not received complement inhibitor treatment prior to study entry. Patients eligible for this trial had to demonstrate high disease activity, defined as LDH level ≥ 1.5 × upper limit of normal (ULN) at screening along with the presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell transfusion due to PNH.

More than 80% of patients in both treatment groups had a history of transfusion within 12 months prior to study entry. The majority of the trial population from the trial with patients not previously treated with complement inhibitors was highly haemolytic at baseline; 86.2% of enrolled patients presented, in the setting of PNH, with elevated LDH ≥ 3 × ULN, a direct measurement of intravascular haemolysis.

Table 9 presents the baseline characteristics of the PNH patients enrolled in the trial of patients not previously treated with complement inhibitors. No apparent clinically meaningful differences were observed between the treatment arms.

Table 9: Baseline characteristics in trial of patients not previously treated with complement inhibitors

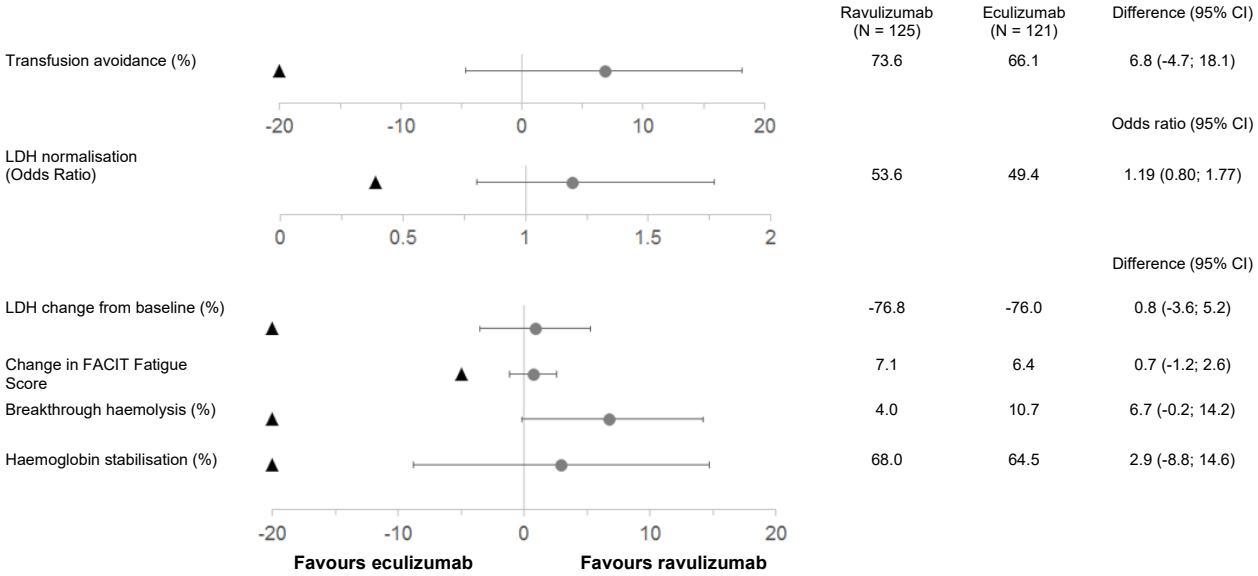
Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Age (years) at PNH diagnosis	Mean (SD) Median Min; Max.	37.9 (14.90) 34.0 15; 81	39.6 (16.65) 36.5 13; 82
Age (years) at first infusion in trial	Mean (SD) Median Min; Max.	44.8 (15.16) 43.0 18; 83	46.2 (16.24) 45.0 18; 86
Sex (n, %)	Male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

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

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

Ravulizumab was non-inferior compared to eculizumab for both coprimary endpoints, avoidance of packed red blood cell transfusion in accordance with protocol-specified guidelines and LDH normalisation from day 29 to day 183, and for all 4 key secondary endpoints (Figure 1).

Figure 1: Analysis of coprimary and secondary endpoints – full analysis set (trial with patients not previously treated with complement inhibitors)



NB: Black triangles indicate the non-inferiority margins; grey dots indicate point estimates.
NB: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

Trial of adult PNH patients previously treated with eculizumab

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

The PNH medical history was similar for ravulizumab and eculizumab treatment groups. The 12-month transfusion history was similar for ravulizumab and eculizumab treatment groups and more than 87% of patients in both treatment groups had not received a transfusion within 12 months prior to study entry. The mean total PNH red blood cell clone size was 60.05%, mean total PNH granulocyte clone size was 83.30%, and the mean total PNH monocyte clone size was 85.86%.

Table 10 presents the baseline characteristics of the PNH patients enrolled in the trial of patients previously treated with eculizumab. No apparent clinically meaningful differences were observed between the treatment arms.

Table 10: Baseline characteristics in trial of patients previously treated with eculizumab

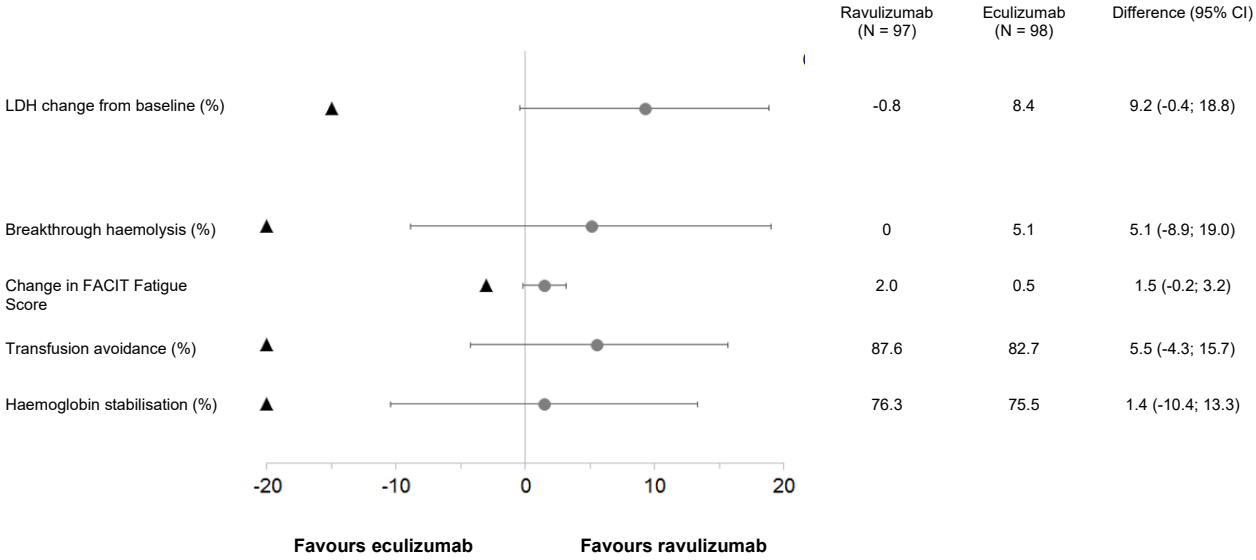
Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min; Max.	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in trial	Mean (SD) Median Min; Max.	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female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

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

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

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

Figure 2: Analysis of coprimary and secondary endpoints – full analysis set (trial with patients previously treated with eculizumab)



NB: Black triangles indicate the non-inferiority margins; grey dots indicate point estimates.
NB: LDH = lactate dehydrogenase; CI = confidence interval.

Atypical haemolytic uraemic syndrome (aHUS)

Study in adult patients with aHUS

The study in adults was a multicentre, single arm, phase 3 clinical study in patients with documented aHUS who had not had any treatment with a complement inhibitor prior to inclusion in this study and showed signs of thrombotic microangiopathy (TMA). The study consisted of a 26-week initial evaluation period and the patients had the option of participating in an extension of up to 4.5 years. A total of 58 patients with documented aHUS were included. The inclusion criteria excluded patients who had TMA resulting from thrombotic thrombocytopenic purpura (TTP) or Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS). Two patients were excluded from the complete analysis set because of a confirmed diagnosis of STEC-HUS. At the start of the study, 93% of the patients showed extrarenal (cardiovascular, pulmonary, central nervous, gastrointestinal, cutaneous or musculoskeletal) signs or symptoms of aHUS.
Table 11 shows the demographic characteristics and baseline characteristics of 56 adult patients who were included in study ALXN1210-aHUS-311 and formed the complete analysis set.

Table 11: Baseline characteristics in the study in adults

Parameter	Statistics	Ravulizumab (N = 56)
Age at first infusion (years)	Mean (SD) Min., Max.	42.2 (14.98) 19.5; 76.6
Sex male	 n (%)	 19 (33.9)
Race[a] Asian White Other	n (%)	 15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelet count (× 10^9/L)	n Median (min., max.)	56 95.25 (18; 473)
Blood haemoglobin (g/L)	n Median (min., max.)	56 85.00 (60.5; 140)
Serum LDH (U/L)	n Median (min., max.)	56 508.00 (229.5; 3,249)
eGFR (mL/min/1.73 m2)	n (%) Median (min., max.)	55 10.00 (4; 80)
Dialysis patients	N (%)	29 (51.8)
Post-partum patients	N (%)	8 (14.3)

Note: the percentages are based on the total number of patients.
Abbreviations: aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; Max. = maximum; Min. = minimum.

The primary endpoint was the complete response of the TMA during the 26-week period for the first assessment, proved by normalisation of the haematological parameters (platelet count ≥ 150 × 10^9/L and LDH ≤ 246 U/l) and an improvement in serum creatinine by ≥ 25% compared with the baseline value. Patients had to fulfil each criterion for a complete response of the TMA at 2 different assessments separated by an interval of at least 4 weeks (28 days) and at each measurement in between.

A complete response of the TMA was observed in 30 of the 56 patients (53.6%) during the 26-week period for the first assessment, as shown in Table 12.

Table 12: Analysis of the complete response of the TMA and the components of the complete response of the TMA during the 26-week period for the first assessment (ALXN1210-aHUS-311)

	Total	Responders	
		n	Fraction (95% CI)[a]
Complete response of the TMA	56	30	0.536 (0.396; 0.675)
Components of the complete response of the TMA			
Normalisation of the platelet count	56	47	0.839 (0.734; 0.944)
Normalisation of LDH	56	43	0.768 (0.648; 0.887)
≥25% improvement in the serum creatinine compared with baseline	56	33	0.589 (0.452; 0.727)
Normalisation of the blood values	56	41	0.732 (0.607; 0.857)

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

Four further patients showed a complete response of the TMA, which was confirmed after the 26-week period for the first assessment (the complete response of the TMA was observed on days 169,

302, 401 and 407). Thus, a total of 34 out of 56 patients showed a complete response of the TMA (60.7%; 95% CI: 47.0%, 74.4%). The number for the response of individual components increased to 48 patients (85.7%; 95% CI: 75.7%, 95.8%) for the normalisation of the platelet count, to 47 patients (83.9%; 95% CI: 73.4%, 94.4%) for the normalisation of LDH, and to 35 patients (62.5%; 95% CI: 48.9%, 76.1%) for improvement in kidney function.

A complete response of the TMA was achieved within a median period of 86 days (7 to 169 days). An increase in the mean platelet count was observed soon after the start of ravulizumab treatment, a rise from 118.52 × 10^9/L at the start of the study to 240.34 × 10^9/L on day 8 being observed. The value remained above 227 × 10^9/L at all subsequent visits during the period for the first assessment (26 weeks). Similarly, the mean LDH value decreased from the baseline value during the first 2 months of treatment, and the decrease was maintained throughout the period for the first assessment (26 weeks).

Of the patients who presented with stage 5 chronic kidney disease, 67.6% (23/34) showed an improvement in the chronic kidney disease of 1 or more stages. The stage of the chronic kidney disease continued to improve in many patients (19/30) after a complete response of the TMA was achieved during the 26-week period for the first assessment. Of the 29 patients who were dialysis-dependent at the time of inclusion in the study, 17 were able to discontinue dialysis treatment by the end of the available follow-up period, while 6 out of 27 patients who were not receiving any dialysis treatment at the start of the study were receiving dialysis treatment at the last available follow-up examination. Table 13 summarises the secondary efficacy results from study ALXN1210-aHUS-311.

Table 13: Secondary efficacy result for study ALXN1210-aHUS-311

Parameter	Study ALXN1210-aHUS-311 (N = 56)	
Haematological parameters in TMA, day 183 Platelet count (10^9/L) Mean (SD) Median Serum LDH (U/L) Mean (SD) Median	Observed value (n = 48) 237.96 (73.528) 232.00 194.46 (58.099) 176.50	Change from baseline (n = 48) 114.79 (105.568) 125.00 -519.83 (572.467) -310.75
≥ 20 g/L increase in haemoglobin from baseline with a confirmatory result by the end of the period for the first assessment m/n Fraction (95% CI)**	40/56 0.714 (0.587; 0.842)	
Change from baseline in CKD stage, day 183 Improvement[a] m/n Fraction (95% CI)* Deterioration[b] m/n Fraction (95% CI)*	32/47 0.681 (0.529; 0.809) 2/13 0.154 (0.019; 0.454)	
eGFR (mL/min/1.73 m2), day 183 Mean (SD) Median	Observed value (n = 48) 51.83 (39.162) 40.00	Change from baseline (n = 47) 34.80 (35.454) 29.00

Note: n: number of patients with available data for a defined examination at the visit on day 183. m: number of patients who meet a defined criterion. The stage of the chronic kidney disease (CKD) is determined using the chronic kidney disease stage classification of the National Kidney Foundation. Stage 5 is the worst category, whereas stage 1 is the best category. The baseline value is determined using the last available eGFR before the start of treatment. Improvement/deterioration: compared with the CKD stage at the start of the study. *The 95% confidence intervals (95% CI) are based on the exact Clopper-Pearson confidence interval. [a]Excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them. [b]Excludes patients with stage 5 at the start of the study, as no deterioration is possible in them.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Generalised Myasthenia Gravis (gMG)

Study in adult patients with gMG

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

Patients with gMG (diagnosed at least 6 months previously) and a positive serologic test for anti-acetylcholine receptor (AChR) antibodies, MGFA (Myasthenia Gravis Foundation of America) clinical classification Class II to IV and remaining symptomatology as evidenced by a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 6 were randomised to treatment with either ravulizumab (N = 86) or placebo (N = 89). Patients on immunosuppressant therapies (corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus)

were permitted to continue on this previous therapy throughout the course of the study. In addition, a rescue therapy (including high dose corticosteroid, PE/PP or IVIg) was allowed if a patient experienced clinical deterioration, as defined by the study protocol.

A total of 162 (92.6%) patients completed the 26-week randomised-controlled period of Study ALXN1210-MG-306. The characteristics of patients at baseline are presented in Table 14. The overwhelming majority of patients included in the study (97%) had been treated with at least one immunomodulatory therapy, including immunosuppressant therapies, PE/PP or IVIg, in the last two years prior to enrolment.

Table 14: Baseline disease characteristics in study ALXN1210-MG-306

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

[a] Prior MG crisis information was collected as part of medical history and not evaluated as per the clinical protocol definition.
[b] Immunosuppressant therapies include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus.
Abbreviations: Max = maximum; min = minimum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis; SD = standard deviation

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

The secondary endpoints, which also assessed changes from baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score, the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores respectively, and changes in quality-of-life assessments.

Ravulizumab demonstrated a statistically significant change in the MG-ADL total score compared to placebo. Primary and secondary endpoints are presented in Table 15.

Table 15: Analysis of primary and secondary efficacy endpoints

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

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

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

Table 16 shows an overview of patients with clinical deterioration and patients requiring rescue therapy over the 26-week randomised-controlled period.

Table 16: Clinical deterioration and rescue therapy

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

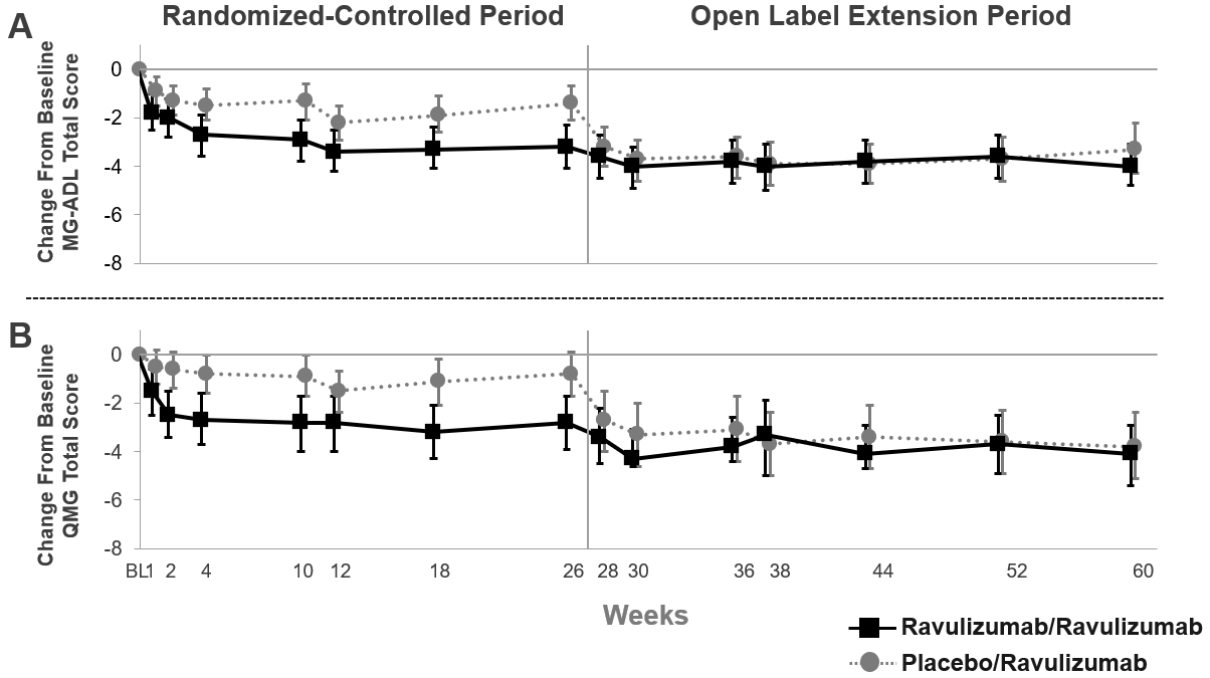
[a] Rescue therapy included high-dose corticosteroid, plasma exchange/plasmapheresis or intravenous immunoglobulin.

At the time of the analysis, 150 of the 158 patients who entered the open-label extension period were still participating in the study.

In patients who initially received ULTOMIRIS during the randomised-controlled period and continued to receive ULTOMIRIS during the first 26 weeks of the open-label extension period, the treatment effect was sustained (Figure 3). In patients who initially received placebo during the 26-week

randomised-controlled period and commenced treatment with ULTOMIRIS during the open-label extension period, a rapid and sustained treatment response was observed (Figure 3).

Figure 3: Change in MG-ADL total score (A) and QMG total score (B) compared to baseline within the randomised-controlled period up to and including week 60 (mean and 95% CI)



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

In the open-label extension period of the study, clinicians had the option to adjust immunosuppressant therapies. In the patients who were observed for 34 weeks in the open-label extension period, 28.0% of patients decreased their daily dose of corticosteroid therapy and 6.2% of patients stopped corticosteroid therapy. The most common reason for change in corticosteroid therapy was an improvement in MG symptoms during treatment with ravulizumab.

Neuromyelitis optica spectrum disorder (NMOSD)

Study in adult patients with NMOSD

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

Study ALXN1210-NMO-307 enrolled 58 adult patients with NMOSD who had a positive serologic test for anti-AQP4 antibodies, at least 1 relapse in the last 12 months prior to the screening period, and an Expanded Disability Status Scale (EDSS) score of ≤ 7. Prior treatment with immunosuppressant therapies (ISTs) was not required for enrolment and 51.7% of patients were on ravulizumab monotherapy. Patients on an established IST (i.e. corticosteroids, azathioprine, mycophenolate mofetil, tacrolimus) were permitted to continue on therapy in combination with ravulizumab, with the requirement for stable dosing until they reached Week 106 of the study. In addition, acute therapy for

relapse treatment (including high-dose corticosteroids, PE/PP, and IVIg) was allowed if a patient experienced a relapse during the study.

Patients included in the study had a median age of 47.4 (18-74) years and most of them were female (90%). Median age at initial clinical presentation of NMOSD was 42.5 years, ranging from 16 to 73 years.

Table 17: Patient disease history and baseline characteristics in study ALXN1210-NMO-307

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

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

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

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

Safety and efficacy in paediatric patients

Paroxysmal nocturnal haemoglobinuria (PNH)

Study in paediatric patients with PNH

The paediatric study (ALXN1210-PNH-304) is a multicentre, open-label, Phase 3 study conducted in children and adolescents with PNH who had either received previous treatment with eculizumab or had not previously been treated with a complement inhibitor. From interim results, a total of 13 paediatric PNH patients completed treatment with ravulizumab during the primary evaluation period (26 weeks) of study ALXN1210-PNH-304. Five of the 13 patients had never been treated with a complement inhibitor and 8 patients had received treatment with eculizumab prior to study entry. Most of the patients were between 12 and 17 years of age at first infusion (mean age: 14.4 years), with two patients under 12 years of age (11 and 9 years). Eight of the 13 patients were female. The mean weight at baseline was 56 kg; the range was 37 to 72 kg. Table 18 shows the disease history and characteristics of the paediatric patients enrolled in study ALXN1210-PNH-304 at baseline.

Table 18: Disease History and Characteristics at Baseline (Full Analysis Set)

Variable	**Patients not previously treated with complement inhibitors** (N = 5)	**Patients previously treated with eculizumab** (N = 8)
Total PNH red blood cell clone size (%) Median (min., max.)	(N = 4) 40.05 (6.9; 68.1)	(N = 6) 71.15 (21.2; 85.4)
Total PNH granulocyte clone size (%) Median (min., max.)	78.30 (36.8; 99.0)	91.60 (20.3; 97.6)
Number of patients with packed red blood cell/whole blood transfusions within 12 months prior to the first dose, n (%)	2 (40.0)	2 (25.0)
Number of packed red blood cell/whole blood transfusions within 12 months prior to the first dose Total Median (min.; max.)	10 5.0 (4; 6)	2 1.0 (1; 1)
Units of packed red blood cells/whole blood transfused within 12 months prior to first dose Total Median (min., max.)	14 7.0 (3; 11)	2 2.0 (2; 2)
Patients with PNH-related disorders prior to patient information and informed consent, n (%) Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Other[a]	5 (100) 2 (40.0) 2 (40.0) 3 (60.0) 2 (40.0) 0	8 (100) 5 (62.5) 5 (62.5) 1 (12.5) 2 (25.0) 1 (12.5)
Pre-treatment LDH levels (U/L) Median (min., max.)	588.50 (444; 2269.7)	251.50 (140.5; 487)

[a] Other PNH-related disorders were reported as “renal and splenic infarcts” and “multiple lesions suggestive of an embolic process”.
Note: percentages are based on the total number of patients in each cohort.
Abbreviations: LDH = lactate dehydrogenase; max. = maximum; min. = minimum; PNH = paroxysmal nocturnal haemoglobulinuria.

The patients received a loading dose of ravulizumab based on body weight 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 were receiving treatment with eculizumab at study entry, Day 1 of the study treatment was planned for 2 weeks after the patient's last dose of eculizumab.

The weight-based dose regimen of ravulizumab provided immediate, complete and sustained terminal complement inhibition throughout the 26-week primary evaluation period, irrespective of whether the patients had received prior treatment with eculizumab. Following initiation of ravulizumab treatment, steady-state therapeutic serum concentrations of ravulizumab were achieved immediately after the first dose and maintained throughout the 26-week primary evaluation period in both cohorts. No breakthrough haemolysis events occurred during the study and no patients had post-baseline free C5 concentrations above 0.5 µg/mL. The mean percentage change in LDH from baseline was -47.91% on Day 183 in the cohort not previously treated with a complement inhibitor and remained stable during the 26-week primary evaluation period in the cohort previously treated with eculizumab. Sixty percent (3/5) of patients not previously treated with a complement inhibitor and 75% (6/8) of patients previously treated with eculizumab achieved haemoglobin stabilisation by Week 26. Transfusion avoidance was achieved in 84.6% (11/13) of patients during the 26-week primary evaluation period. These interim efficacy results are presented in Table 19 below.

Table 19: Interim efficacy results from the clinical study in paediatric PNH patients (ALXN1210-PNH-304) - 26-week primary evaluation period

Endpoint	**Ravulizumab (no previous treatment with complement inhibitors, N = 5)**	**Ravulizumab (switch, previously treated with complement inhibitors, N = 8)**
LDH percentage change from baseline Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion avoidance percentage (95% CI)	60.0 (14.66; 94.73)	100.0 (63.06; 100.00)
Haemoglobin stabilisation percentage (95% CI)	60.0 (14.66; 94.73)	75 (34.91; 96.81)
Breakthrough haemolysis (%)	0	0

Abbreviations: LDH = lactate dehydrogenase

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

Atypical haemolytic uraemic syndrome (aHUS)

The use of Ultomiris in paediatric patients for the treatment of aHUS is supported by the results of a clinical study in children and adolescents (in total, 31 patients with documented aHUS were included. 28 patients aged 10 months to 17 years were included in the complete analysis set).

Study in paediatric patients with aHUS

This paediatric study was a 26-week, continuous, multicentre, single arm, phase 3 study in children and adolescents.

In total, 21 patients without previous eculizumab treatment with the documented diagnosis of aHUS and evidence of TMA were included in the study; of these, 18 were included in the complete analysis set. The inclusion criteria excluded patients who had TMA resulting from TTP and STEC-HUS. Two patients received one single dose and one patient received two doses; the patients then stopped the treatment and were excluded from the complete analysis set, because the aHUS was not confirmed.

The mean body weight at the start of the study was 22.2 kg; the majority of the patients were in the weight category ≥ 10 to < 20 kg at the start of the study. Most patients (72.2%) showed extrarenal (cardiovascular, pulmonary, central nervous, gastrointestinal, cutaneous or musculoskeletal) signs or symptoms of aHUS before treatment at the start of the study. 33.3% (n = 6) of the patients had stage 5 CKD at the start of the study.

A total of 10 patients who were switching from eculizumab to ravulizumab and had a documented aHUS diagnosis and signs of TMA were included in the study. A clinical response to eculizumab had to be present before the patients were included in the study (i.e. LDH < 1.5 × ULN and platelet count ≥ 150,000/µL and eGFR > 30 mL/min/1.73 m^2). Consequently, there are no data on the use of ravulizumab in patients who do not respond to eculizumab.

Table 20 shows the baseline characteristics of paediatric patients who were included in study ALXN1210-aHUS-312.

Table 20: Demographic characteristics and baseline characteristics in study ALXN1210-aHUS-312

Parameter	Statistics	Ravulizumab (no previous treatment, N = 18)	Ravulizumab (treatment switch, N = 10)
Age group at first infusion (years) Birth to < 2 years 2 to < 6 years 6 to < 12 years 12 to < 18 years	n (%)	 2 (11.1) 9 (50.0) 5 (27.8) 2 (11.1)	 1 (10.0) 1 (10.0) 1 (10.0) 7 (70.0)
Sex male	n (%)	 8 (44.4)	 9 (90.0)
Ethnicity[a] Native American (Indian) or Alaskan Asian Black or African American White Unknown	n (%)	 1 (5.6) 5 (27.8) 3 (16.7) 9 (50.0) 1 (5.6)	 0 (0.0) 4 (40.0) 1 (10.0) 5 (50.0) 0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelet count (× 10^9/L)	Median (min., max.)	51.25 (14; 125)	281.75 (207; 415.5)
Haemoglobin (g/L)	Median (min., max.)	74.25 (32; 106)	132.0 (114.5; 148)
LDH (U/L)	Median (min., max.)	1,963.0 (772; 4,985)	206.5 (138.5; 356)
eGFR (mL/min/1.73 m^2)	Median (min., max.)	22.0 (10; 84)	99.75 (54; 136.5)
Dialysis dependence at the start of the study	n (%)	6 (33.3)	0 (0.0)

Note: the percentages are based on the total number of patients.
[a] The patients may have several ethnicities.
Abbreviations: aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; Max. = maximum; Min. = minimum.

The primary endpoint was the complete response of the TMA during the 26-week period for the first assessment, determined on the basis of the normalisation of the haematological parameters (platelet count ≥ 150 × 10^9/L and LDH ≤ 246 U/l) and an improvement in serum creatinine of ≥ 25% compared with the baseline value. Patients had to fulfil all criteria for a complete response of the TMA at 2 different assessments separated by an interval of at least 4 weeks (28 days) and at each measurement in between.

A complete response of the TMA was observed during the 26-week period for the first assessment in 14 of the 18 patients without previous treatment (77.8%), as shown in Table 21.

Table 21: Complete response of the TMA and analysis of the components of the complete response of the TMA during the 26-week period for the first assessment (ALXN1210-aHUS-312)

	Total	Responders	
		n	Fraction (95% CI)a
Complete response of the TMA	18	14	0.778 (0.524; 0.936)
Components of the complete response of the TMA			
Normalisation of the platelet count	18	17	0.944 (0.727; 0.999)
Normalisation of LDH	18	16	0.889 (0.653; 0.986)
≥25% improvement in the serum creatinine compared with baseline	18	15	0.833 (0.586; 0.964)
Normalisation of the blood values	18	16	0.889 (0.653; 0.986)

Note: 1 patient withdrew from the study after treatment with 2 doses of ravulizumab.
[a] The 95% confidence intervals (95% CI) for the fraction were based on the asymptotic Gaussian approximation method with continuity correction.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

The complete response of the TMA during the period for the first assessment was achieved in a median time of 30 days (15 to 97 days). In all patients with a complete response of the TMA, the response was maintained throughout the period for the first assessment, continuous improvements in kidney function being observed. After the start of the ravulizumab treatment, a rise in the mean platelet count was soon detectable, with an increase from 60.50 × 10^9/L at the start of the study to 296.67 × 10^9/L on day 8; it was above 296 × 10^9/L at all subsequent visits in the period for the first assessment (26 weeks).

Three further patients showed a complete response of the TMA, which was confirmed after the 26-week period for the first assessment (the complete response of the TMA was observed on days 291, 297 and 353). Thus, 17 of the 18 paediatric patients (94.4%) (95% CI: 72.7%; 99.9%) showed a complete response of the TMA. The response of individual components increased to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for the normalisation of the platelet count, to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for the normalisation of LDH, and to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for improvement in kidney function.

All 6 patients who were dialysis-dependent at inclusion in the study were able to discontinue the dialysis treatment. In five of these patients, this was possible on day 43 at the latest. No patient started dialysis treatment during the study. Most of the patient population (15/17) showed an improvement in the CKD of one or more stages by day 183; 14 patients showed an improvement of 2 or more stages. Table 22 summarises the secondary efficacy results for study ALXN1210-aHUS-312.

Table 22: Secondary efficacy results of study ALXN1210-aHUS-312

Parameter	Study ALXN1210-aHUS-312 (N = 18)	
Haematological parameters in TMA, day 183 Platelet count (10^9/L) Mean (SD) Median Serum LDH (U/L) Mean (SD) Median	Observed value (n = 17) 304.94 (75.711) 318.00 262.41 (59.995) 247.00	Change from baseline (n = 17) 245.59 (91.827) 247.00 -2,044.13 (1,328.059) -1,851.50
≥ 20 g/L increase in haemoglobin from baseline with confirmed result during the period for the first assessment m/N Fraction (95% CI)*	16/18 0.889 (0.653; 0.986)	
Change from baseline in CKD stage, day 183 Improvement[a] m/n Fraction (95% CI)* Deterioration[b] m/n Fraction (95% CI)*	15/17 0.882 (0.636; 0.985) 0/11 0.000 (0.000; 0.285)	
eGFR (mL/min/1.73 m2), day 183 Mean (SD) Median	Observed value (n = 17) 108.5 (56.87) 108.00	Change from baseline (n = 17) 85.4 (54.33) 80.00

Note: n: number of patients with available data for a defined examination at the visit on day 183. m: number of patients who meet a defined criterion. The stage of the chronic kidney disease (CKD) is determined using the chronic kidney disease stage classification of the National Kidney Foundation. Stage 1 is regarded as the best category, whereas stage 5 is the worst category. The baseline value is determined using the last available eGFR before the start of treatment. Improvement/deterioration: compared with the CKD stage at the start of the study.
*The 95% confidence intervals (95% CI) are based on the exact Clopper-Pearson confidence interval.
[a] Improvement excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them.
[b] Deterioration excludes patients with stage 5 at the start of the study, as no deterioration is possible in them.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

In patients who were previously treated with eculizumab, the switch to ravulizumab led to maintenance of control of the disease, as can be seen from the stable haematological and renal parameters, without any evident impact on safety.

The efficacy of ravulizumab in the treatment of aHUS seems to be similar in paediatric patients to that in adult patients.

Pharmacokinetics

Absorption

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

Distribution

The mean (standard deviation [SD]) central volume and volume of distribution at steady state for adult patients and paediatric patients with PNH and aHUS and in adult patients with gMG and NMOSD are presented in Table 25.

Metabolism

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolised in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Ravulizumab contains only naturally occurring amino acids and has no known active metabolites.

Elimination

The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in adult and paediatric patients with PNH or aHUS and adult patients with gMG or NMOSD are presented in Table 23.

Table 23: Estimated central volume, distribution, biotransformation and elimination parameters following ravulizumab administration

	Adult and paediatric patients with PNH	**Adult and paediatric patients with aHUS**	**Adult patients with gMG**	**Adult patients with NMOSD**
Estimated central volume (litres) Mean (SD)	Adults: 3.44 (0.65) Paediatrics: 2.87 (0.60)	Adults: 3.25 (0.61) Paediatrics: 1.14 (0.51)	3.42 (0.756)	2.91 (0.571)
Volume of distribution at steady state (litres) Mean (SD)	5.30 (0.9)	5.22 (1.85)	5.74 (1.16)	4.77 (0.819)
Terminal elimination half-life (days) Mean (SD)	49.6 (9.1)	51.8 (16.2)	56.6 (8.36)	64.3 (11.0)
Clearance (litres/day) Mean (SD)	0.08 (0.022)	0.08 (0.04)	0.08 (0.02)	0.05 (0.016)

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

Linearity/non-linearity

Over the studied range of dosing and dosing regimens, ravulizumab exhibited dose-proportional and time-linear pharmacokinetics (PK).

Kinetics in specific patient groups

Body weight

Body weight is a significant co-variable in patients with PNH, aHUS gMG and NMOSD, which leads to lower bioavailability in heavier patients. Weight-based dosing is given in section "Dosage/Administration", Table 1, Table 2 and Table 3.

No formal trial of the effect of sex, ethnic background, age (geriatric patients), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on a pharmacokinetic population analysis, no impact of sex, age, ethnic background and hepatic or renal function on the pharmacokinetic properties of ravulizumab was identified in the studied healthy volunteer subjects and patients with PNH, aHUS, gMG or NMOSD. As a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab were investigated in aHUS patients with different degrees of kidney function impairment, including dialysis-dependent patients. In these patient subpopulations, including patients with proteinuria, no differences in the pharmacokinetics were observed.

Preclinical data

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

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

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

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products.
Dilution should be carried out using only sodium chloride 9 mg/mL (0.9%) solution for injection as diluent.

Shelf life

The medicinal product may be used only up to the date marked with "EXP" on the container.

Shelf life after opening

Ultomiris 300 mg/3 mL and 1100 mg/11 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 2–8 °C and up to 4 hours at room temperature.

Ultomiris 300 mg/30 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 2–8 °C and up to 6 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2–8ºC).
Do not freeze.
Keep the container in the outer carton to protect contents from light (and/or moisture).
Keep out of the reach of children.
For storage conditions after dilution of the medicinal product, see section "Shelf life after opening".

Instructions for handling

Each vial is intended for single use only.

Ultomiris 300 mg/3 mL and 1100 mg/11 mL
Ultomiris must be diluted to a final concentration of 50 mg/mL.
The usual aseptic conditions must be observed.

Prepare Ultomiris as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section "Dosage/Administration".
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. Mix the product carefully. Do not shake.
4. After dilution, the final concentration of the solution to be infused is 50 mg/mL.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2–8 °C. If stored at 2–8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus

injection. Refer to Table 4 and Table 5 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.

6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2–8 °C or 4 hours at room temperature, taking into account the expected infusion time.

Table 24: Loading dose administration reference table for Ultomiris 300 mg/3 mL and 1100 mg/11 mL

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

[a] Body weight at time of treatment.

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

Table 25: Maintenance dose administration reference table for Ultomiris 300 mg/3 mL and 1100 mg/11 mL

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

[a] Body weight at time of treatment.

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

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

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

[a] Body weight at time of treatment

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

Ultomiris 300 mg/30 mL

Ultomiris must be diluted to a final concentration of 5 mg/mL.

The usual aseptic conditions must be observed.

Prepare Ultomiris as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section "Dosage/Administration".
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. Mix the product carefully. Do not shake.
4. After dilution, the final concentration of the solution to be infused is 5 mg/mL.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2–8°C. If stored at 2–8°C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to Table 6 and Table 7 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2–8°C or 6 hours at room temperature, taking into account the expected infusion time.

Table 27: Loading dose administration reference table for Ultomiris 300 mg/30 mL

Body weight (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	900	90	90	180
≥ 30 to < 40	1,200	120	120	240
≥ 40 to < 60	2,400	240	240	480
≥ 60 to < 100	2,700	270	270	540
≥ 100	3,000	300	300	600

[a] Body weight at time of treatment.

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

Table 28: Maintenance dose administration reference table for Ultomiris 300 mg/30 mL

Body weight (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	2,100	210	210	420
≥ 30 to < 40	2,700	270	270	540
≥ 40 to < 60	3,000	300	300	600
≥ 60 to < 100	3,300	330	330	660
≥ 100	3,600	360	360	720

[a] Body weight at time of treatment.

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

Table 29: Supplemental dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion

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

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

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

Authorisation number

67278 (Swissmedic)

Packs

Ultomiris 300 mg/3 mL (100 mg/mL) concentrate for solution for infusion

3 mL sterile concentrate in a type I glass vial contains 300 mg ravulizumab (A)

Ultomiris 1100 mg/11 mL (100 mg/mL) concentrate for solution for infusion

11 mL sterile concentrate in a type I glass vial contains 1100 mg ravulizumab (A)

Ultomiris 300 mg/30 mL (10 mg/mL) concentrate for solution for infusion

30 mL sterile concentrate in a type I glass vial contains 300 mg ravulizumab (A)

Marketing authorisation holder

Alexion Pharma GmbH
Giesshübelstrasse 30
8045 Zurich
Switzerland

Date of revision of the text

April 2023