

Date: 4 April 2025

Swissmedic, Swiss Agency for Therapeutic Products

# ***Swiss Public Assessment Report***

## ***Extension of therapeutic indication***

### **Ultomiris**

**International non-proprietary name:** ravulizumab

**Pharmaceutical form:** concentrate for solution for infusion

**Dosage strength(s):** 300 mg/3 mL; 1100 mg/11 mL;  
300 mg/30 mL

**Route(s) of administration:** intravenous use

**Marketing authorisation holder:** Alexion Pharma GmbH

**Marketing authorisation no.:** 67278

**Decision and decision date:** approved on 16 February 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.

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## 1 Terms, Definitions, Abbreviations

AChR	Acetylcholine Receptor
aHUS	Atypical haemolytic uraemic syndrome
EMA	European Medicines Agency
gMG	Generalised myasthenia gravis
IV	Intravenous
kg	Kilogram
MAH	Marketing authorisation holder
PNH	Paroxysmal nocturnal haemoglobinuria
q8w	once every 8 weeks
RMP	Risk management plan
SwissPAR	Swiss Public Assessment Report
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)

#### 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.

#### Orphan drug status

The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a<sup>decies</sup> no. 1 TPA. Orphan drug status was granted on 23 June 2022.

#### Authorisation as human medicinal product in accordance with Article 13 TPA

The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

### 2.2 Indication and dosage

#### 2.2.1 Requested indication

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

#### 2.2.2 Approved indication

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

#### 2.2.3 Requested dosage

The body weight-based ravulizumab treatment regimen proposed for adult patients with gMG is identical to the one approved for PNH and aHUS, which includes a loading dose on Day 1, followed by maintenance doses on Day 15 and every 8 weeks (q8w) thereafter, administered by IV infusion (Table 1).

**Table 1: Ravulizumab Weight-Based Dosing Regimen**

Body Weight	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60 kg	2400	3000
≥ 60 to < 100 kg	2700	3300
≥ 100 kg	3000	3600

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

#### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

Application	22 August 2022
Formal control completed	19 September 2022
Preliminary decision	20 December 2022
Response to preliminary decision	28 December 2022
Final decision	16 February 2023
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the European Medicines Agency (EMA). This Swiss Public Assessment Report (SwissPAR) relates to the publicly available assessment report Ultomiris, EMEA/H/C/004954/II/0026, issued by the EMA.

### **3 Nonclinical aspects**

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Ultomiris, EMEA/H/C/004954/II/0026, issued by the EMA.

## 4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The clinical aspects in this SwissPAR refer to the publicly available assessment report Ultomiris, EMEA/H/C/004954/II/0026, issued by the EMA.

## **5 Risk management plan summary**

The Risk Management Plan (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.



## 6 Appendix

### Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for Healthcare Professionals for Ultomiris, concentrate for solution for infusion 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](http://www.swissmedicinfo.ch)).

#### Note:

The following Information for Healthcare Professionals has been translated by the Marketing Authorisation Holder (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.

### Dosage/Administration

Ravulizumab must be administered by healthcare professionals and under the supervision of a physician experienced in the treatment of patients with haematological disorders, kidney diseases or neuromuscular disorders.

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 or gMG

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 ( $\geq 18$  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  $\pm 7$  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
$\geq 40$ to $< 60$	2,400	3,000	Every 8 weeks
$\geq 60$ to $< 100$	2,700	3,300	Every 8 weeks
$\geq 100$	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
$\geq 40$ to $< 60$	2,400	1,200	600
	3,000	1,500	
$\geq 60$ to $< 100$	2,700	1,500	600
	3,300	1,800	
$\geq 100$	3,000	1,500	600
	3,600	1,800	
<b>Timing of ravulizumab supplemental dose</b>		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, 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 or gMG 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 elderly patients with PNH or aHUS in clinical studies.

### *Children and adolescents*

Children and adolescents with PNH and aHUS weighing  $\geq 40$  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  $\geq 10$  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.

#### *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) <sup>a</sup>	Loading dose (mg)	Minimum infusion time Minutes (hours)	Maintenance dose (mg)	Minimum infusion time Minutes (hours)
≥ 10 to < 20 <sup>b</sup>	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30 <sup>b</sup>	900	35 (0.6)	2100	75 (1.3)
≥ 30 to < 40 <sup>b</sup>	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)

<sup>a</sup> Body weight at the time of treatment.

<sup>b</sup> 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) <sup>a</sup>	Supplemental dose <sup>b</sup> (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)

<sup>a</sup> Body weight at time of treatment.

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

<sup>a</sup> Body weight at time of treatment.

<sup>b</sup> For PNH and aHUS indications only

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

Body weight range (kg) <sup>a</sup>	Supplemental dose <sup>b</sup> (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)

<sup>a</sup> Body weight at time of treatment.

<sup>b</sup> 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").

### 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%). These reactions were mild to moderate in severity and transient, including lower back pain, drop in blood pressure, rise in blood pressure, 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.

### 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.

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

### **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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 ( $\geq 1/10$ )	Common ( $\geq 1/100$ , $< 1/10$ )	Uncommon ( $\geq 1/1000$ , $< 1/100$ )
<b>Gastrointestinal disorders</b>	Diarrhoea, nausea	Vomiting, abdominal pain, dyspepsia	
<b>General disorders and administration site conditions</b>	Fatigue	Pyrexia, influenza-like illness, asthenia	Chills
<b>Immune system disorders</b>			Hypersensitivity· anaphylactic reaction <sup>a</sup>
<b>Infections and infestations</b>	Infection of the upper respiratory tract, nasopharyngitis		Meningococcal infection <sup>b</sup> , gonococcal infection <sup>c</sup>
<b>Injury, poisoning and procedural complications</b>		Infusion-related reaction	
<b>Musculoskeletal and connective tissue disorders</b>		Arthralgia, back pain, myalgia, muscle spasms	
<b>Nervous system disorders</b>	Headache	Dizziness	
<b>Skin and subcutaneous tissue disorders</b>		Urticaria <sup>a</sup> , pruritus, rash	

<sup>a</sup> Estimated from post-marketing experience

<sup>b</sup> Meningococcal infection includes preferred terms of meningococcal infection and meningococcal sepsis

<sup>c</sup> Gonococcal infection includes disseminated gonococcal infection

### *Description of selected undesirable effects*

#### *Meningococcal infection/sepsis*

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, 3 out of 261 adult PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ravulizumab; all 3 had been vaccinated. All 3 recovered while continuing treatment with ravulizumab. In the clinical study in children and adolescents with PNH, no meningococcal infections occurred among the 13 patients treated with ravulizumab. In clinical studies of aHUS, no meningococcal infections occurred in any of the 89 patients who received treatment with ravulizumab. In the gMG study, no meningococcal infections occurred among the 86 patients receiving treatment with ravulizumab during the randomised-controlled period. Please refer to 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. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to 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) and in the gMG study (N=86), only two cases (0.45%) 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 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.

### 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 EIViS portal (Electronic Vigilance System). You can obtain information about this at [www.swissmedic.ch](http://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 and in adult patients with gMG 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 and gMG 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.

### *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  $\geq 1.5 \times$  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  $\geq 3 \times$  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 Mean (SD) Median	925 9.0 (7.74) 6.0	861 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 <sup>a</sup> before trial start	n (%)	121 (96.8)	120 (99.2)
Anaemia		103 (82.4)	105 (86.8)
Haematuria or haemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anaemia		41 (32.8)	38 (31.4)
Renal failure		19 (15.2)	11 (9.1)
Myelodysplastic syndrome		7 (5.6)	6 (5.0)
Pregnancy complication		3 (2.4)	4 (3.3)
Other <sup>b</sup>		27 (21.6)	13 (10.7)

<sup>a</sup> Based on medical history.

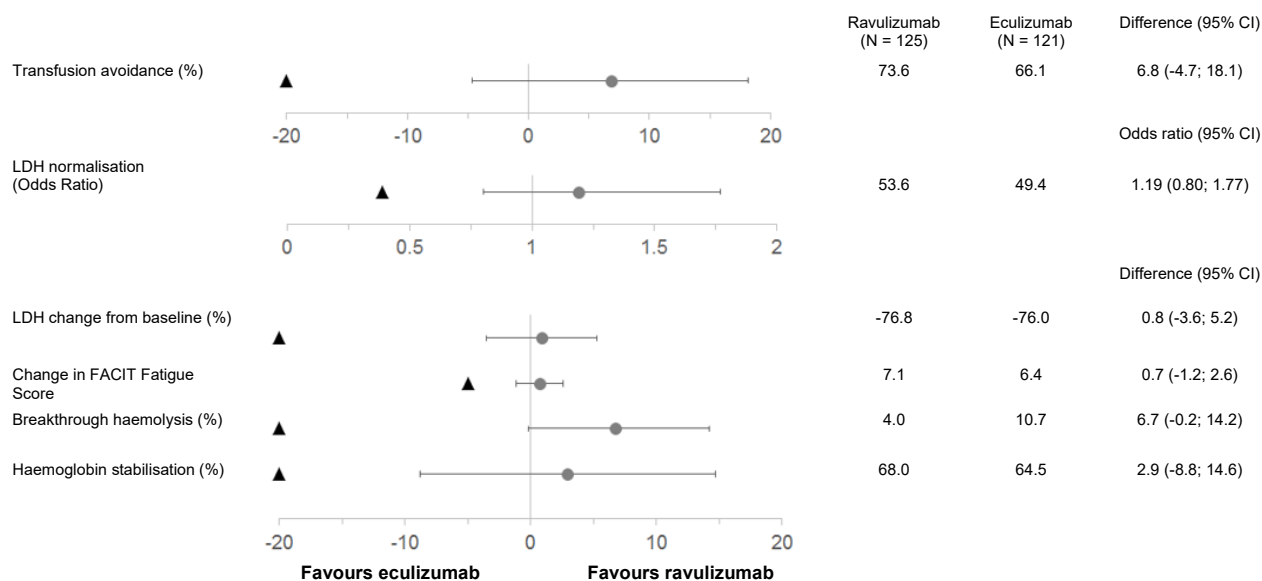
<sup>b</sup> "Other" as specified on case report form included thrombocytopenia, chronic kidney disease and pancytopenia, as well as a number of other symptoms and disorders.

The coprimary endpoints were transfusion avoidance, and haemolysis as directly measured by normalisation of LDH levels (LDH levels  $\leq 1 \times$  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 ( $\text{LDH} \leq 1.5 \times \text{ULN}$ ) 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 <sup>a</sup> before trial start	n (%)	90 (92.8)	96 (98.0)
Anaemia		64 (66.0)	67 (68.4)
Haematuria or haemoglobinuria		47 (48.5)	48 (49.0)
Aplastic anaemia		34 (35.1)	39 (39.8)
Renal failure		11 (11.3)	7 (7.1)
Myelodysplastic syndrome		3 (3.1)	6 (6.1)
Pregnancy complication		4 (4.1)	9 (9.2)
Other <sup>b</sup>		14 (14.4)	14 (14.3)

<sup>a</sup> Based on medical history.

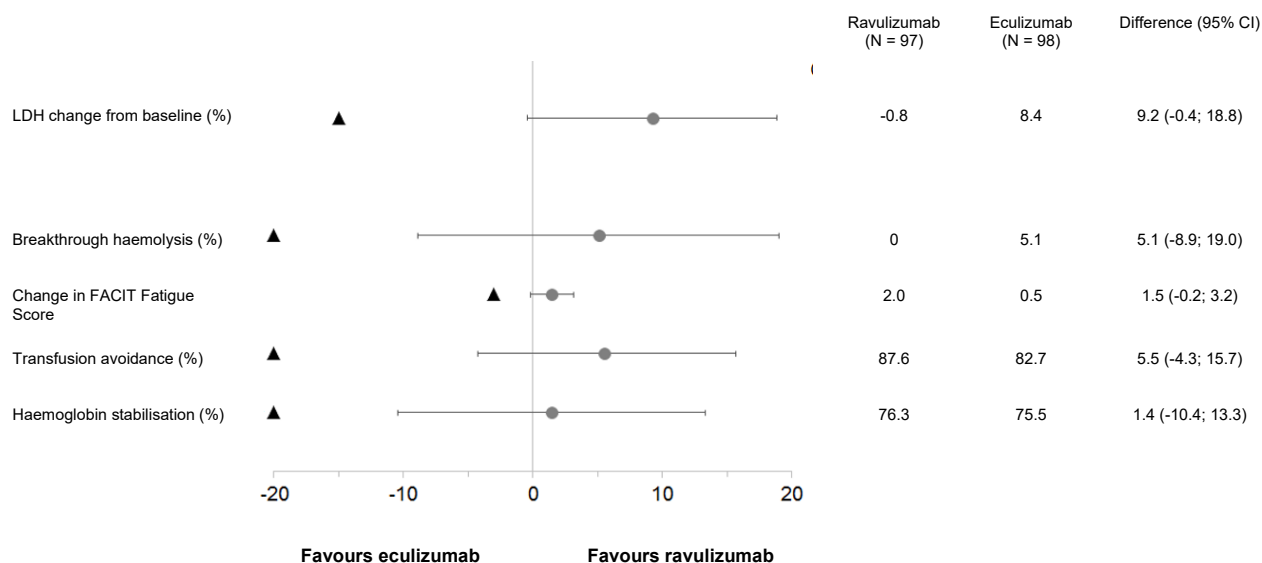
<sup>b</sup> "Other" category included neutropenia, renal dysfunction and thrombopenia, as well as a number of other symptoms and disorders.

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 <sup>a</sup> Asian White Other	n (%)	15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelet count ( $\times 10^9/L$ )	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 m <sup>2</sup> )	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  $\geq 150 \times 10^9/L$  and LDH  $\leq 246$  U/l) and an improvement in serum creatinine by  $\geq 25\%$  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) <sup>a</sup>
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)
$\geq 25\%$ 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)

<sup>a</sup> 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  $118.52 \times 10^9/\text{L}$  at the start of the study to  $240.34 \times 10^9/\text{L}$  on day 8 being observed. The value remained above  $227 \times 10^9/\text{L}$  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)	
	Observed value (n = 48)	Change from baseline (n = 48)
Haematological parameters in TMA, day 183		
Platelet count (10 <sup>9</sup> /L)		
Mean (SD)	237.96 (73.528)	114.79 (105.568)
Median	232.00	125.00
Serum LDH (U/L)		
Mean (SD)	194.46 (58.099)	-519.83 (572.467)
Median	176.50	-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	40/56	
Fraction (95% CI)**	0.714 (0.587; 0.842)	
Change from baseline in CKD stage, day 183		
Improvement <sup>a</sup>		
m/n	32/47	
Fraction (95% CI)*	0.681 (0.529; 0.809)	
Deterioration <sup>b</sup>		
m/n	2/13	
Fraction (95% CI)*	0.154 (0.019; 0.454)	
eGFR (mL/min/1.73 m <sup>2</sup> ), day 183	Observed value (n = 48)	Change from baseline (n = 47)
Mean (SD)		
Median	51.83 (39.162)	34.80 (35.454)
	40.00	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. <sup>a</sup>Excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them. <sup>b</sup>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  $\geq 6$  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)
<b>Sex</b>	n (%)		
Male		44 (49.4)	42 (48.8)
Female		45 (50.6)	44 (51.2)
<b>Age at first dose of study drug (years)</b>	Mean (SD) (min, max)	53.3 (16.05) (20, 82)	58.0 (13.82) (19, 79)
<b>Elderly (<math>\geq 65</math> years of age) at study entry</b>	n (%)	24 (27.0)	30 (34.9)
<b>Duration of MG since diagnosis (years)</b>	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
<b>Baseline MG-ADL Score</b>	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
<b>Baseline QMG Score</b>	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
<b>Baseline MGFA classification</b>	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)
<b>Any prior intubation since diagnosis (MGFA Class V)</b>	n (%)	9 (10.1)	8 (9.3)

<b>Number of patients with prior MG crisis since diagnosis<sup>a</sup></b>	<b>n (%)</b>	<b>17 (19.1)</b>	<b>21 (24.4)</b>
<b>Number of stable immunosuppressant therapies<sup>b</sup> at study entry</b>	<b>n (%)</b>		
0		8 (9.0)	10 (11.6)
1		34 (38.2)	40 (46.5)
≥ 2		47 (52.8)	36 (41.9)

<sup>a</sup> Prior MG crisis information was collected as part of medical history and not evaluated as per the clinical protocol definition.

<sup>b</sup> 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**

<b>Efficacy Endpoints at Week 26</b>	<b>Placebo (N = 89) LS Mean (SEM)</b>	<b>Ravulizumab (N = 86) LS Mean (SEM)</b>	<b>Statistic for Comparison</b>	<b>Treatment Effect (95% CI)</b>	<b>p-value (Using Mixed Effect Repeated Measures)</b>
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 <sup>a</sup>

<sup>a</sup> 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**



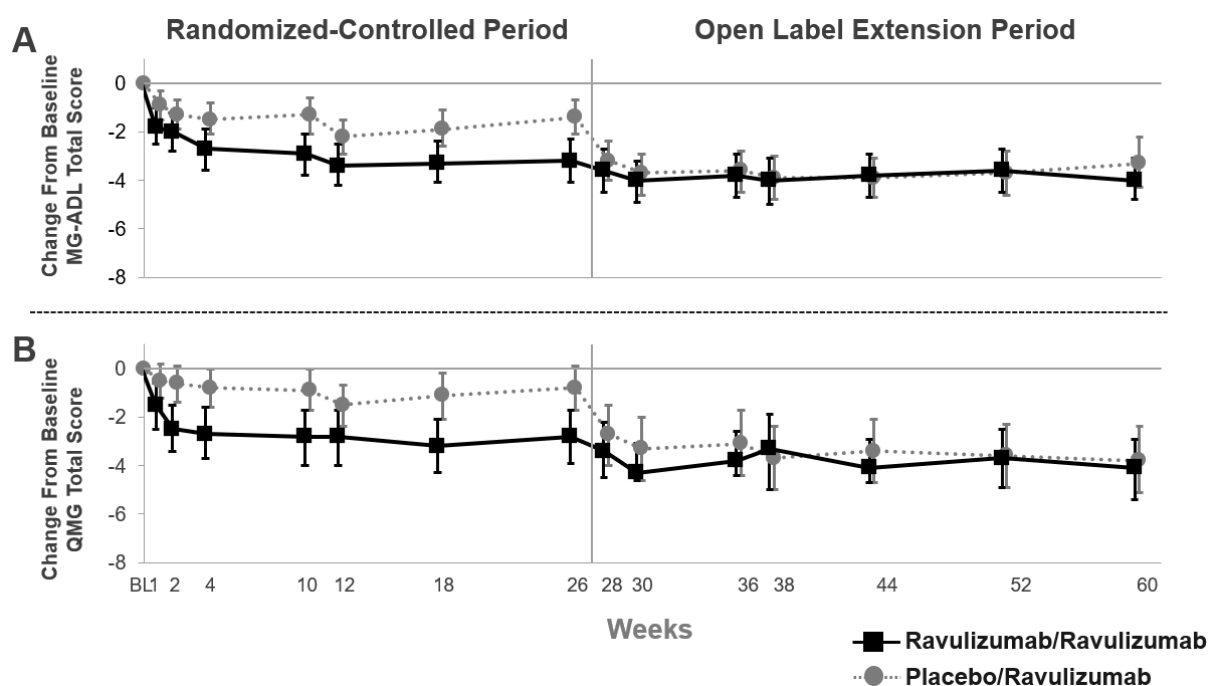
Variable	Statistic	Placebo (N = 89)	Ravulizumab (N = 86)
Total number of patients with clinical deterioration	n (%)	15 (16.9)	8 (9.3)
Total number of patients requiring rescue therapy <sup>a</sup>	n (%)	14 (15.7)	8 (9.3)

<sup>a</sup> 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.

## 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 17](#) shows the disease history and characteristics of the paediatric patients enrolled in study ALXN1210-PNH-304 at baseline.

**Table 17: 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 (%)	5 (100)	8 (100)
Anaemia	2 (40.0)	5 (62.5)
Haematuria or haemoglobinuria	2 (40.0)	5 (62.5)
Aplastic anaemia	3 (60.0)	1 (12.5)
Renal failure	2 (40.0)	2 (25.0)
Other <sup>a</sup>	0	1 (12.5)
Pre-treatment LDH levels (U/L) Median (min., max.)	588.50 (444; 2269.7)	251.50 (140.5; 487)

<sup>a</sup> 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 haemoglobinuria.

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  $\geq 20$  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  $\mu\text{g/mL}$ . 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 18 below.

**Table 18: 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  $\geq 10$  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  $< 1.5 \times$  ULN and platelet count  $\geq 150,000/\mu\text{L}$  and eGFR  $> 30 \text{ mL/min/1.73 m}^2$ ). Consequently, there are no data on the use of ravulizumab in patients who do not respond to eculizumab.

Table 19 shows the baseline characteristics of paediatric patients who were included in study ALXN1210-aHUS-312.

**Table 19: 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)	n (%)		
Birth to < 2 years		2 (11.1)	1 (10.0)
2 to < 6 years		9 (50.0)	1 (10.0)
6 to < 12 years		5 (27.8)	1 (10.0)
12 to < 18 years		2 (11.1)	7 (70.0)
Sex	n (%)		
male		8 (44.4)	9 (90.0)
Ethnicity <sup>a</sup>	n (%)		
Native American (Indian) or Alaskan		1 (5.6)	0 (0.0)
Asian		5 (27.8)	4 (40.0)
Black or African American		3 (16.7)	1 (10.0)
White		9 (50.0)	5 (50.0)
Unknown		1 (5.6)	0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelet count ( $\times 10^9/L$ )	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 <sup>2</sup> )	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.

<sup>a</sup> 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  $\geq 150 \times 10^9/L$  and LDH  $\leq 246$  U/l) and an improvement in serum creatinine of  $\geq 25\%$  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 20.

**Table 20: 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) <sup>a</sup>
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.

<sup>a</sup> 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  $60.50 \times 10^9/L$  at the start of the study to  $296.67 \times 10^9/L$  on day 8; it was above  $296 \times 10^9/L$  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 21 summarises the secondary efficacy results for study ALXN1210-aHUS-312.

**Table 21: Secondary efficacy results of study ALXN1210-aHUS-312**

Parameter	Study ALXN1210-aHUS-312 (N = 18)	
Haematological parameters in TMA, day 183	Observed value (n = 17)	Change from baseline (n = 17)
Platelet count (10 <sup>9</sup> /L)		
Mean (SD)	304.94 (75.711)	245.59 (91.827)
Median	318.00	247.00
Serum LDH (U/L)		
Mean (SD)	262.41 (59.995)	-2,044.13 (1,328.059)
Median	247.00	-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 <sup>a</sup>		
m/n	15/17	
Fraction (95% CI)*	0.882 (0.636; 0.985)	
Deterioration <sup>b</sup>		
m/n	0/11	
Fraction (95% CI)*	0.000 (0.000; 0.285)	
eGFR (mL/min/1.73 m <sup>2</sup> ), day 183	Observed value (n = 17)	Change from baseline (n = 17)
Mean (SD)		
Median	108.5 (56.87) 108.00	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.

<sup>a</sup> Improvement excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them.

<sup>b</sup> 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 (t<sub>max</sub>) 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 adult patients with gMG are presented in Table 22.

### 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 patients with PNH, adult and paediatric patients with aHUS and adult patients with gMG are presented in Table 22.

**Table 22: 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
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)
Volume of distribution at steady state (litres) Mean (SD)	5.30 (0.9)	5.22 (1.85)	5.74 (1.16)
Terminal elimination half-life (days) Mean (SD)	49.6 (9.1)	51.8 (16.2)	56.6 (8.36)
Clearance (litres/day) Mean (SD)	0.08 (0.022)	0.08 (0.04)	0.08 (0.02)

Abbreviations: aHUS = atypical haemolytic uremic syndrome; gMG = generalized myasthenia gravis; 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 and gMG, 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 or gMG. 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 (2–8°C).

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

Body weight (kg) <sup>a</sup>	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment.

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

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

Body weight (kg) <sup>a</sup>	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment.

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

**Table 25: 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) <sup>a</sup>	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment<sup>b</sup> 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 26: Loading dose administration reference table for Ultomiris 300 mg/30 mL**

Body weight (kg) <sup>a</sup>	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment.

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

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

Body weight (kg) <sup>a</sup>	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment.

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

**Table 28: Supplemental dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion**

Body Weight Range (kg) <sup>a</sup>	Supplemental dose (mg)	ULTOMIRIS volume (mL)	Volume of NaCl diluent <sup>b</sup> (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

<sup>a</sup> Body weight at time of treatment

<sup>b</sup> 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

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Switzerland

### **Date of revision of the text**

December 2022