NATIONAL PHARMACEUTICAL REGULATORY DIVISION (NPRA)
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY FOR NEW REGISTRATION APPLICATION (ORPHAN DRUG)

PRODUCT NAME:
Ultomiris 100mg/mL Concentrate For Solution For Infusion (MAL24096028ACRZ)

ACTIVE INGREDIENT:
Ravulizumab 100mg/mL

PRODUCT REGISTRATION HOLDER:
AstraZeneca Sdn. Bhd.

PRODUCT MANUFACTURER:
Alexion Pharma International Operations Limited, Dublin, Ireland

APPROVAL DATE:
5 September 2024 (DCA 400)

1.0 BACKGROUND INFORMATION

a. Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9.
b. Ravulizumab is structurally related to eculizumab (Soliris®) but differs from eculizumab at 4 amino acid substitutions in the heavy chain. These substitutions are intended to enable an extended dosing interval by increasing the circulating half-life.
c. The designation of Orphan Medicine for Ultomiris®, for PNH (D59.5), aHUS (D58.8), and Myasthenia gravis (G70.0) was approved in the Drug Evaluation Committee Meeting 06/2023 (Mesyuarat JKPP 06/2023; date of designation: 5th July 2023).

1.1 PROPOSED INDICATION:

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

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

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

1.2 PROPOSED POSOLOGY:

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

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. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

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

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

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

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)*	Dosing Interval

≥ 40 to < 60	2,400	3,000	Every 8 weeks
≥ 60 to < 100	2,700	3,300	Every 8 weeks
≥ 100	3,000	3,600	Every 8 weeks

* First maintenance dose is administered 2 weeks after loading dose

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

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

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

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

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

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

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

In gMG patients, treatment with ravulizumab has only been studied in the setting of chronic administration.

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

<u>Special populations</u>

Elderly

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

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic impairment

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

Paediatric population
Paediatric patients with PNH and aHUS with body weight ≥ 40 kg are treated in accordance with the adult dosing recommendations (Table 1). The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg are shown in Table 3.

For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses should be administered per weight-based dosing regimen shown in Table 3, starting 2 weeks after loading dose administration.

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

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

* First maintenance dose is administered 2 weeks after loading dose

Data to support safety and efficacy of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in “Undesirable effects” but no recommendation on a posology can be made for patients below 10 kg body weight.

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

Ravulizumab has not been studied in paediatric patients with gMG.

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

Table 4: Dose administration rate for Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Body Weight Range (kg)[a]	Loading Dose (mg)	Minimum Infusion Duration Minutes (hours)	Maintenance Dose (mg)	Minimum Infusion Duration Minutes (hours)
≥ 10 to < 20[b]	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30[b]	900	35 (0.6)	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 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

1.4 Route of Administration

Intravenous infusion.

1.5 Pharmacological Aspects

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AJ02

Pharmacodynamic properties

Ravulizumab is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Pharmacokinetic Properties:

Absorption

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

Distribution

The mean (standard deviation [SD]) central volume and volume of distribution at steady state for adult and paediatric patients with PNH and aHUS, and adult patients with gMG are presented in Table 6.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in adult patients with PNH, adult and paediatric patients with aHUS and adult patients with gMG are presented in Table 6.

Table 6: 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 (liters), 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 (liters), 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 (liters/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 dose and regimen range, ravulizumab exhibited dose proportional and time linear pharmacokinetics (PK).

Special populations

Weight

Body weight is a significant covariate in patients with PNH, aHUS and gMG, resulting in lower exposures in heavier patients. Weight-based dosing is proposed in “Posology”, Table 1, Table 2 and Table 3.

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

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

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Ravulizumab is a recombinant humanized IgG2/4 monoclonal antibody consisting of two identical heavy chains and light chains linked by disulphide bonds. Ravulizumab was constructed by introducing four unique mutations into the heavy chain of eculizumab (Soliris).
- Process validation had been submitted for 3 consecutive batches from the Lonza Biologics Porrino (LBP), Spain site while there are 4 consecutive batches submitted from Alexion Pharma International Operations Limited, Ireland (ADMF) site. All parameters monitored during the validation were within their respective pre-defined ranges.
- The proposed shelf life for DS is for 18 months at 2-8^{o}C (LBP site only) or 30 months at -25 to -15^{o}C. The stability data submitted supports the proposed shelf life. Comprehensive comparability study between LBP and ADMF demonstrated that both sites produced comparable drug substance.
- The GMP certificate for the drug substance manufacturer for LBP site was issued by Competent Regional Authority, Spain while the GMP certificate for ADMF site was issued by Health Products Regulatory Authority, Ireland.

2.1.2 Finished Product

- Process validation had been submitted for 2 batches of 11ml and 3 batches of 3ml and all met pre-defined acceptance criteria for AAMF site. Process validation was also submitted for Catalent site for 6 batches (4 batches 11ml, 2 batches 3ml) and all met predefined acceptance criteria. The bracketing approach is justified because it is considered as one manufacturing process that uses the same flow to fill two presentations (3ml and 11ml). The product composition and concentrations are identical.
- DP comparability was assessed by comparing release data from 6 batches from Catalent against a set of comparator lots manufactured at AAMF. The results showed that the quality of DP at the Catalent site is comparable to AAMF.
- The proposed shelf life for unopened vial is for 18 months at 2-8^{o}C. Stability data had been submitted from AAMF and Catalent and support the storage condition. After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product using ULTOMIRIS 100 mg/mL have been demonstrated for up to 24 hours at 2°C – 8°C and up to 4 hours at 25^{o}C.
- Ultomiris is supplied as a sterile aqueous solution for IV administration at concentration of 100mg/ml in stoppered 3ml and 11ml Type I glass vials. It is designed for infusion by diluting into commercially available normal saline.
- The GMP certificate for the drug product manufacturer for AAMF site was issued by Health Products Regulatory Authority, Ireland while the GMP for Catalent Indiana was verified by US FDA.
- The protocol of analysis and validation data have been evaluated and were found satisfactory based on the documentation submitted.

2.2 Non-Clinical

- A total of 14 studies (5 in vitro and 9 in vivo studies) were conducted as part of the ravulizumab non-clinical development programme. In vivo studies consisted of 1 pharmacodynamic (mice), 2 pharmacokinetic (monkey & rabbit) and 6 toxicology studies (5 mice and 1 rabbit).
- Five toxicology studies were pivotal safety studies conducted at sites in United States, in accordance with Organisation for Economic Co-operation and Development (OECD) GLPs.
- PK/PD studies carried out demonstrated longer half-life and PD effect relative to eculizumab.

- Toxicological characterization was acceptable and no maternal or fetal toxicities were observed in ravulizumab treated animal models.

2.3 Clinical

2.3.1 Efficacy

Table 7: Summary of pivotal clinical studies conducted

<table>
<tr><th>Study Type & Design</th><th>Objective</th><th>Results</th></tr>
<tr><td colspan="3">PNH</td></tr>
<tr><td>Study ALXN1210-PNH-301

Open-label, randomised, active-controlled, multicentre, phase 3 trial

N = 246
Ultomiris: 125
Soliris: 121</td><td>To assess the noninferiority of Ultomiris (ravulizumab) compared to Soliris (eculizumab) in adult patients with PNH who had never been treated with a complement inhibitor.</td><td>Table 8: Co-primary endpoint results
<table>
<tr><th>Co-primary Endpoint</th><th>ULTOMIRIS (n=125)</th><th>SOLIRIS (n=121)</th><th>Difference (95% CI)</th></tr>
<tr><td>Transfusion avoidance (%)*</td><td>73.6</td><td>66.1</td><td>6.8 (-4.7, 18.1)</td></tr>
<tr><td>LDH-Normalization (Odds Ratio)**</td><td>53.6</td><td>49.4</td><td>1.19 (0.80, 1.77)</td></tr>
</table>
*The lower bound of the 95% CI of the treatment difference was greater than the protocol-specified NIM of -20%.
**The lower bound of the 95% CI was greater than the protocol-specified NIM of 0.39.

Conclusion:
The favorable benefit/risk profile of Ultomiris in this study supports its use for the treatment of complement inhibitor-naïve patients with PNH. For both coprimary endpoints, Ultomiris achieved statistically significant noninferiority compared to Soliris at Week 26.</td></tr>
<tr><td>Study ALXN1210-PNH-302

CHAMPION 302

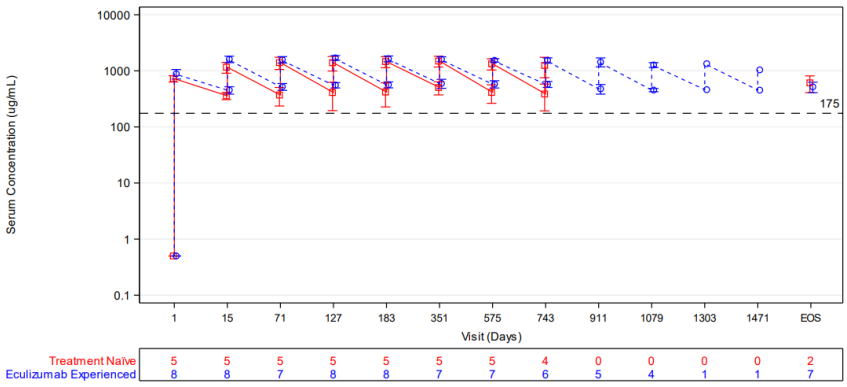
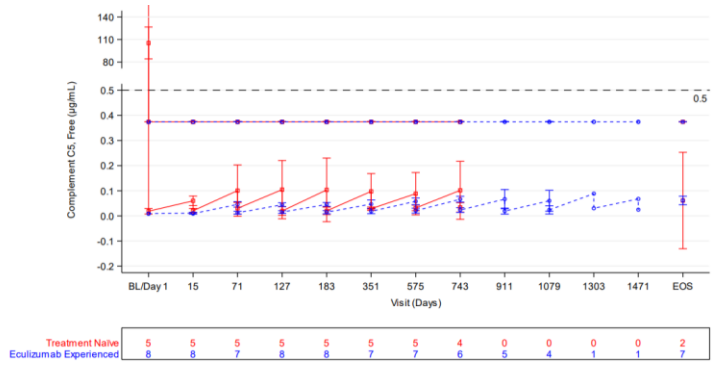
Open-label, randomised, active-controlled, multicentre, phase 3 trial

N = 195
Ultomiris: 97
Soliris: 98</td><td>To assess the noninferiority of Ultomiris compared to Soliris in adult patients with PNH who were clinically stable after having been treated with Soliris for at least the past 6 months.</td><td>Table 9: Lactate Dehydrogenase (LDH)-Change from Baseline (%)
<table>
<tr><th>Primary Endpoint</th><th>ULTOMIRIS (n=97)</th><th>SOLIRIS (n=98)</th><th>Difference (95% CI)</th></tr>
<tr><td>LDH-Change from Baseline (%)</td><td>-0.8</td><td>8.4</td><td>-9.2
(-18.8, 0.4)</td></tr>
</table>
The upper bound of the 95% CI for the difference was less than than the protocol-specified NIM (Ultomiris minus Soliris) of 15%.

Conclusion:
The primary endpoint, percent change in LDH from baseline to Week 26, met the primary objective of statistically significant noninferiority of Ultomiris compared to Soliris. The point estimate for the difference between treatment groups favored Ultomiris. The favorable benefit/risk profile of Ultomiris in this study demonstrates that patients with PNH can be safely and effectively switched from Soliris to Ultomiris.</td></tr>
<tr><td>Study ALXN1210-PNH-304 (paeds)

Open-label, uncontrolled, single-arm, multicentre, phase 3 trial

N = 13
Complement Inhibitor</td><td>To assess the PK, PD, safety, and efficacy of Ultomiris in pediatric patients with PNH.</td><td>Primary Efficacy Endpoint (PK)</td></tr>
</table>

Study Type & Design	Objective	Results
Treatment-Naïve Patients: 5 Soliris-Experienced Patients: 8		Figure 1: Mean (SD) Serum Ultomiris Concentration Versus Time for Complement Inhibitor Treatment-Naïve and Eculizumab Experienced Cohorts, Semi-Log Scale  Note: The dashed horizontal line indicates serum concentration of 175 µg/mL. Day 71 sample from 1 patient was processed incorrectly (pre- and post- samples combined in same cryovial), therefore, was not shipped to the central laboratory. Day 1 (predose) sample for 1 patient and Day 351 (predose) sample for 1 patient was regarded as implausible and removed. Abbreviations: EOS = End of Study; SD = standard deviation All ravulizumab C_{trough} levels were above the threshold for C5 inhibition (175 µg/mL), except for 1 patient. Mean serum ravulizumab concentration at steady state was comparable in the eculizumab-experienced patients to the complement inhibitor treatment-naïve patients **Primary Efficacy Endpoint (PD)** Figure 2: Mean (95% CI) Serum Free C5 Concentration Over Time  Note: Baseline was defined as the last non-missing value prior to first dose of ravulizumab. For the free C5 BLOQ values, LLOQ/2 = 0.00915 µg/mL was utilized. The dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL. Day 71 sample for 1 patient was processed incorrectly (predose and postdose samples were combined in the same cryovial) and, therefore, it was not shipped to the central laboratory. Abbreviations: BL = baseline; BLOQ = below limit of quantification; C5 = complement component 5; CI = confidence interval; LLOQ = lower limit of quantification None of the Soliris-experienced patients had a serum free C5 concentration ≥ 0.5 µg/mL (threshold associated with complete inhibition of C5 activity) at Baseline or any visit during the study. All of the complement inhibitor treatment-naïve patients had serum free C5 concentrations ≥ 0.5 µg/mL at Baseline and none had such a concentration once treatment with Ultomiris was initiated. Thus, Ultomiris provided complete and sustained complement inhibition, which occurred immediately in complement inhibitor treatment-naïve patients. **Secondary efficacy endpoint: % change in LDH from Baseline to Week 26 in complement inhibitor treatment-naïve cohort**

<table>
<tr><th>Study Type & Design</th><th>Objective</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Variable</th><th>Mean Difference</th></tr>
<tr><td>LDH-Change from Baseline (%)</td><td>-47.91</td></tr>
</table>
In the eculizumab-experienced cohort, the mean percent change from Baseline in LDH remained generally stable during the entire study period.

Conclusion:
Results from this study demonstrates that weight-based Ultomiris treatment met PK/PD objectives and provided immediate, complete, and sustained inhibition of terminal complement regardless of prior experience with Soliris. These results confirm that pediatric patients with PNH can be initiated on Ultomiris or switched from Soliris to Ultomiris safely and with continued efficacy from terminal complement inhibition.</td></tr>
<tr><td colspan="3">aHUS</td></tr>
<tr><td>Study ALXN1210-aHUS-311 (adults)

Open-label, uncontrolled, single arm, multicentre, phase 3 trial

N = 56</td><td>To assess the efficacy of Ultomiris in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA.</td><td>Table 10: Complete thrombotic microangiopathy (TMA) Response
<table>
<tr><th rowspan="2">Primary Endpoint</th><th rowspan="2">Total</th><th colspan="2">Responder</th></tr>
<tr><th>n</th><th>Proportion (95% CI)</th></tr>
<tr><td>Complete TMA Response*</td><td>56</td><td>30</td><td>0.536 (0.396, 0.675)</td></tr>
</table>
*Components of Complete TMA Response: Platelet count normalization, LDH normalization, ≥25% improvement in serum creatinine from baseline. Patients must have met all criteria concurrently, and each criterion must have been met at 2 separate assessments obtained at least 4 weeks apart, and any measurement in between.

Conclusion:
The primary endpoint, complete TMA response during the 26-week Initial Evaluation Period, was achieved by 53.6% of patients. The median time to complete TMA response was 86 days following the first dose of ravulizumab. This supports its use for the treatment of complement inhibitor-naïve adult patients with complement-mediated TMA, including aHUS.</td></tr>
<tr><td>Study ALXN1210-aHUS-312 (paeds)

Open-label, uncontrolled, single-arm, multicentre, phase 3 trial

N = 28

Complement Inhibitor Treatment-Naïve (Cohort 1): 18

Soliris-Experienced (Cohort 2): 10</td><td>To assess the efficacy of Ultomiris in complement inhibitor treatment-naïve pediatric patients (ie, Cohort 1) with aHUS to inhibit complement-mediated TMA.</td><td>Table 11: Complete TMA Response in Cohort 1
<table>
<tr><th rowspan="2">Primary Endpoint</th><th rowspan="2">Total</th><th colspan="2">Responder</th></tr>
<tr><th>n</th><th>Proportion (95% CI)</th></tr>
<tr><td>Complete TMA Response*</td><td>18</td><td>14</td><td>0.778 (0.524, 0.936)</td></tr>
</table>
*Components of Complete TMA Response: Platelet count normalization, LDH normalization, ≥25% improvement in serum creatinine from baseline. Patients must have met all criteria concurrently, and each criterion must have been met at 2 separate assessments obtained at least 4 weeks apart, and any measurement in between.

Conclusion:
• The primary endpoint, complete TMA response, was achieved by 77.8% of patients in Cohort 1. The median time to complete TMA response was 30 days following the first dose of Ultomiris.
• Hematologic parameters in Cohort 2 patients remained stable throughout the Initial Evaluation Period.
This supports its use for the treatment of pediatric patients with aHUS, regardless of experience with prior complement inhibitor treatment.</td></tr>
<tr><td colspan="3">gMG</td></tr>
</table>

<table>
<tr><th>Study Type & Design</th><th>Objective</th><th>Results</th></tr>
<tr><td>Study ALXN1210-MG-306

CHAMPION MG

Open-label, randomised, double-blind, placebo-controlled, multicentre phase 3 trial

N = 175
Ultomiris: 86
Placebo: 89

Patients on immunosuppressant therapies were permitted to continue on therapy.</td><td>To assess the efficacy of Ultomiris compared with placebo in the treatment of AChR antibody-positive gMG based on the improvement in the MG-ADL profile in complement-inhibitor naïve adult patients.</td><td>Table 12: MG-ADL total score Change from Baseline (%) at Week 26
<table>
<tr><th>Primary Endpoint</th><th>ULTOMIRIS (n=86)</th><th>Placebo (n=89)</th><th>Difference (95% CI)</th><th>p-value</th></tr>
<tr><td>MG-ADL total score from Baseline (LS mean, SEM)</td><td>-3.1 (0.38)</td><td>-1.4 (0.37)</td><td>-1.6 (-2.6, -0.7)</td><td>0.0009</td></tr>
</table>
Conclusion:
This study met its primary objective by demonstrating the statistically significant superiority of Ultomiris over placebo in MG-ADL total score. Treatment with Ultomiris resulted in a statistically significant reduction in MG-ADL total score from Baseline to Week 26 compared to placebo (p = 0.0009).</td></tr>
</table>

2.3.2 SAFETY

- Overall, the safety profile of Ultomiris is comparable to Soliris with no new safety signals.
- The most common adverse drug reactions for adults (very common frequency) are diarrhoea, upper respiratory tract infection, naspopharyngitis and headaches.
- The safety profile in children were similar to that observed in adults in both PNH and aHUS. The most common adverse reactions reported in pediatric PNH patients were abdominal pain and nasopharyngitis while in pediatric aHUS patients, it was pyrexia.

3.0 CONCLUSION

The Drug Control Authority (DCA) in their 400th meeting on 5th September 2024 has decided to approve the registration of this product with the following indication:

Paroxysmal Nocturnal Hemoglobinuria (PNH)

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

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Atypical Hemolytic Uremic Syndrome (aHUS)

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

Generalized Myasthenia Gravis (gMG)

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