EU RMP	
Drug substance	Ravulizumab
Version number	9
Succession number	3
Data lock point	30 June 2024
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for ULTOMIRIS® (ravulizumab)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

Administrative information

Rationale for submitting an updated RMP*:*

This RMP update is submitted with the revised additional risk minimisation measures for ULTOMIRIS.

Summary of significant changes in this RMP

Part III

The description of the aHUS registry (M11-001) was revised in Section 3.2 to remove SOLIRIS (eculizumab), since the commitment for SOLIRIS was fulfilled and the study remains ongoing for ULTOMIRIS only.

Part V

The revised additional risk minimisation measures in place for ULTOMIRIS were presented in Section 5.2.

Section 5.3 was revised in line with the changes made in Section 5.2 of the RMP.

Part VI

All changes made in the body of document were reflected in the Summary of the RMP, as applicable.

Part VII

The approved key messages for the revised additional risk minimisation measures were provided in Annex 6 to reflect on the changes made in the body of the document in Section 5.2.

Other RMP versions under evaluation	**Version number**: Not applicable **Submitted**: Not applicable **Procedure number**: Not applicable
Details of currently approved RMP	**Version number**: 8 **Approved with procedure**: EMEA/H/C/004954/IB/0046/G **Date of approval:** 04 July 2024

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	**Definition/Explanation**
AChR	Acetylcholine Receptor
ADA	Antidrug Antibodies
aHUS	Atypical Haemolytic Uraemic Syndrome
AQP4	Aquaporin 4
ATC	Anatomical Therapeutic Chemical Classification System
C5	Complement Component 5
CFH	Complement Factor H
CFI	Complement Factor I
CI	Confidence Interval
DIBD	Development International Birth Date
DNA	Deoxynucleic Acid
EEA	European Economic Area
ESRD	End-stage Renal Disease
EU	European Union
GLP	Good Laboratory Practice
gMG	Generalised Myasthenia Gravis
GPI	Glycophosphatidylinositol
HCP	Healthcare Professional
HLA	Human Leukocyte Antigen
HUS	Haemolytic Uraemic Syndrome
IBD	International Birth Date
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INN	International Nonproprietary Name
IPIG	International PNH Interest Group
LETM	Longitudinally Extensive Transverse Myelitis
MAH	Marketing Authorisation Holder
MCP	Membrane Cofactor Protein
MG	Myasthenia Gravis
MuSK	Muscle Specific Kinase
NOEL	No-Observed-Effect Level
NMOSD	Neuromyelitis Optica Spectrum Disorder

Abbreviation/ Special term	**Definition/Explanation**
PIG-A	X-linked Phosphatidylinositol Glycan A Gene
PL	Package Leaflet
PNH	Paroxysmal Nocturnal Haemoglobinuria
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (EU)
STEC	Shiga Toxin Producing *Escherichia coli*
TMA	Thrombotic Microangiopathy
US	United States

1. PART I: PRODUCT(S) OVERVIEW

Table 1-1 Product(s) overview

Active substance(s) (INN or common name)	Ravulizumab
Pharmacotherapeutic group(s) (ATC code)	L04AA43
Marketing Authorisation Holder	Alexion Europe, SAS
Medicinal products to which this RMP refers	3
Invented name(s) in the EEA	ULTOMIRIS
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** ULTOMIRIS is a formulation of ravulizumab, which is a long-acting humanised monoclonal $IgG_{2/4K}$ antibody produced in Chinese hamster ovary cell culture by recombinant DNA technology and consisting of two identical 448 amino acid heavy chains and two identical 214 amino acid light chains and has a molecular weight of approximately 148 kDa.
	Summary of mode of action: Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b-9. By binding specifically to C5, ravulizumab antagonises terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.
	Important information about its composition: Ravulizumab is a humanised monoclonal antibody produced in the Chinese hamster ovary cell culture by recombinant DNA technology.
Hyperlink to the Product Information	ULTOMIRIS, Product Information

Table 1-1 Product(s) overview

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:
Paroxysmal nocturnal haemoglobinuria (PNH)
ULTOMIRIS is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with PNH:
• in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
• in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.
Atypical haemolytic uremic syndrome (aHUS)
ULTOMIRIS is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.
Generalised myasthenia gravis (gMG)
ULTOMIRIS is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.
Neuromyelitis optica spectrum disorder (NMOSD)
ULTOMIRIS is indicated in the treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive.</td></tr>
<tr><td></td><td>Proposed:
Not applicable.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Adult patients with PNH, aHUS, gMG, or NMOSD
The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient’s body weight, as shown in Table A. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after the loading dose administration.
Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab), but the subsequent dose should be administered according to the original schedule.
Table A: Ravulizumab weight-based dosing regimen for adult patients with body weight greater than or equal to 40 kg
<table>
<tr><th>Body weight range (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)*</th><th>Dosing interval</th></tr>
</table>
</td></tr>
</table>

Table 1-1 Product(s) overview

	<table><tr><td>≥ 40 to < 60</td><td>2,400</td><td>3,000</td><td>Every 8 weeks</td></tr><tr><td>≥ 60 to < 100</td><td>2,700</td><td>3,300</td><td>Every 8 weeks</td></tr><tr><td>≥ 100</td><td>3,000</td><td>3,600</td><td>Every 8 weeks</td></tr></table> * First maintenance dose is administered 2 weeks after loading dose. <u>Paediatric patients with PNH and aHUS</u> *Paediatric patients with body weight ≥ 40 kg* These patients should be treated in accordance with the adult dosing recommendations (See Table A). *Paediatric patients with body weight≥ 10 kg to < 40 kg* The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg are shown in Table B. 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 B, starting 2 weeks after loading dose administration. Table B: Ravulizumab weight-based dosing regimen for paediatric patients with PNH or aHUS below 40 kg <table><tr><th>Body weight range (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)*</th><th>Dosing interval</th></tr><tr><td>≥ 10 to < 20</td><td>600</td><td>600</td><td>Every 4 weeks</td></tr><tr><td>≥ 20 to < 30</td><td>900</td><td>2,100</td><td>Every 8 weeks</td></tr><tr><td>≥ 30 to < 40</td><td>1,200</td><td>2,700</td><td>Every 8 weeks</td></tr></table> * First maintenance dose is administered 2 weeks after loading dose.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths in the EEA	**Current:** Concentrate for solution for infusion <u>ULTOMIRIS 300 mg/3 mL concentrate for solution for infusion</u> Translucent, clear to yellowish colour, pH 7.4 solution. Each vial of 3 mL contains 300 mg of ravulizumab (100 mg/mL).

Table 1-1 Product(s) overview

	ULTOMIRIS 1,100 mg/11 mL concentrate for solution for infusion Translucent, clear to yellowish colour, pH 7.4 solution. Each vial of 11 mL contains 1,100 mg of ravulizumab (100 mg/mL). ULTOMIRIS 300 mg/30 mL concentrate for solution for infusion Clear to translucent, slight whitish colour, pH 7.0 solution. Each vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL).
	Proposed: Not appliable.
Is/will the product be subject to additional monitoring in the EU?	No

ATC, anatomical therapeutic chemical classification system; C5, complement component 5; DNA, deoxyribonucleic acid; EEA, European Economic Area; EU, European Union; Ig, immunoglobulin; INN, international non-proprietary name; PNH, paroxysmal nocturnal haemoglobinuria, RMP, risk management plan.

2. PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

2.1.1 Paroxysmal nocturnal haemoglobinuria

Incidence and prevalence:

Epidemiologic studies of the occurrence of paroxysmal nocturnal haemoglobinuria (PNH) are scarce. A regional study of English PNH patients diagnosed by flow cytometry for glycophosphatidylinositol (GPI)-linked antigens from 2004 to 2018, reported an annual incidence of 0.35 per 100,000 person-years (Richards et al 2021). A study from Spain estimated annual incidence at 0.25 per 100,000 person-years utilising a case definition of a laboratory assessment with GPI-deficient cells in ≥ 2 cell lineages at frequencies of > 0.01% of all leukocytes (Morado et al 2017).

Incidence as defined by new PNH diagnoses as defined by International Disease Classification codes was reported as 0.08 (95% confidence interval [CI]: 0.06, 0.11) per 100,000 person-years within the Danish National Register and 0.57 per 100,000 person-years within a large United States (US) employer-sponsored insurance claims database (Hansen et al 2020, Jalbert et al 2019, Richards et al 2021).

Prevalence has been estimated to range from 1.00 to 3.81 per 100,000 persons utilising data from a Danish national registry, US administrative claims database, and a regional study in England (Hansen et al 2020, Jalbert et al 2019, Richards et al 2021).

Demographics of the population in the authorised indication and risk factors for the disease:

PNH can occur at any age, although it is diagnosed most often in the fourth or fifth decade of life (Füreder et al 2020, Lee et al 2013, Schrezenmeier et al 2020, Villegas et al 2017, Yu et al 2016). PNH is considered rare in children although it may manifest in some patients during teenage years (Hill et al 2017). In general, there is a slight female preponderance in PNH, as noted in several registries (Füreder et al 2020, Socie et al 2016, Villegas et al 2017).

In an analysis of 4,439 patients enrolled in the International PNH registry as of July 2017, 53% were female and median age at diagnosis was 35.5 years (Schrezenmeier et al 2020). Overall, 67.9% of patients were from Europe, 14.4% from the US and 17.7% from the rest of the world, including Asia. In this registry, 78.4% of participants were White, 16.3% were Asian, 3% were Black and the remaining 2.3% were another race or unspecified (Schrezenmeier et al 2020).

A separate analysis of this registry, which evaluated Asian and non-Asian patients who were not eculizumab-treated at baseline and who had ≥ 1% PNH clone size, found no statistical difference in age, sex or disease duration between Asian and non-Asian patients (Sakurai et al 2019).

Risk factors

Although PNH has a genetic basis, it is not a heritable condition as it is a somatic mutation of the X-linked phosphatidylinositol glycan A (*PIG-A*) gene that occurs randomly (Sahin et al 2015). Patients who develop PNH often have some bone marrow dysfunction, such as aplastic anaemia or myelodysplastic syndrome, prior to or concurrently at time of PNH diagnosis (Parker 2012, Rachidi et al 2010). The leading theory suggests that many healthy individuals have some GPI-deficient haematopoietic stem cells, which generally do not preferentially replicate. However, some event, enabling GPI-deficient cells to expand in the presence of bone marrow dysfunction, is needed to induce PNH (Parker 2012, Rachidi et al 2010, Sahin et al 2015).

The main existing treatment options:

Prior to the introduction of eculizumab (SOLIRIS®) and ravulizumab (ULTOMIRIS), the treatment of PNH was mainly supportive, aiming to control the clinical manifestations of the disease (management of haemolysis, anaemia, thrombophilia, and bone marrow failure). This supportive treatment included blood transfusion, administration of erythropoiesis-stimulating agents, corticosteroids, or anabolic steroids, iron therapy, thrombosis prophylaxis, and thrombolytic therapy (Al-Ani et al 2016).

Eculizumab, a compound with the same mode of action as ravulizumab, represents a significant breakthrough in the management of PNH, characterised by high efficacy and acceptable safety profile. The efficacy/effectiveness of eculizumab on PNH has markedly changed the management and overall perspective toward this disease in PNH patients (Al-Ani et al 2016), including paediatric patients (Reiss et al 2014). Ravulizumab was designed to provide extended duration of terminal complement inhibition, while retaining the safety, efficacy, and low immunogenicity associated with eculizumab.

The only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation. However, allogeneic haematopoietic stem cell transplantation is associated with high mortality and morbidity. Moreover, because of eculizumab high effectiveness, stem cell transplantation is only considered for cases of severe marrow failure (Al-Ani et al 2016).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

PNH is a chronic disease with serious clinical symptoms leading to poor quality of life, including anaemia, thrombosis, organ damage, kidney disease, hypertension, cardiac dysfunction, dyspnoea, haemoptysis, erectile dysfunction, fatigue, and abdominal pain (Hill et al 2017).

Other serious clinical symptoms lead to poor quality of life in PNH, including anaemia, kidney disease, fatigue, and smooth muscle dystonia (Hill et al 2017). Specific to patients experiencing clinically evident extravascular haemolysis, an additional complication includes iron overload as the result of eculizumab and ravulizumab blocking intravascular haemolysis and subsequently preventing further urinary iron loss (Risitano et al 2019, Röth et al 2011).

Disease burden was high in an analysis of patients enrolled in the International PNH Registry, with 55.8% reporting haemolysis and 42.8% with an impaired estimated glomerular filtration rate at baseline (defined as the date of enrolment for never treated patients and date of eculizumab initiation for patients ever treated with eculizumab). Further, 63% of patients had a history of bone marrow failure and 18.8% had a history of a major adverse vascular event (Schrezenmeier et al 2020). In this registry, commonly reported PNH symptoms included: fatigue (80.9%), dyspnoea (45.3%), haemoglobinuria (45.0%), abdominal pain (35.2%), dysphagia (16.5%), and erectile dysfunction (24.2% of males) (Schrezenmeier et al 2020).

The survival experience of patients with PNH has improved over time though among untreated patients, mortality remains higher as compared to the general population (Hill et al 2017, Jang et al 2016, Kelly et al 2011). Among those patients treated with eculizumab, the survival experience of patients has been demonstrated to be similar to a matched general population (Füreder et al 2020, Kelly et al 2011).

Thromboembolism is generally considered the most common cause of mortality in PNH patients, accounting for approximately 40% to 67% of deaths with a known cause (Devos et al 2018, Heitlinger 2013, Hill et al 2013).

An analysis of the International PNH Registry found that the history of thromboembolism was significantly lower in Asian patients compared to non-Asian patients (3.6% compared to 8.9%) (Sakurai et al 2019).

An analysis of published studies across the US/Europe and Asia found similar rates of mortality in each region, but different leading causes of death by region (Yu et al 2016).

In Western countries, thromboembolism was the leading cause of death, followed by serious infections, malignant tumours, haemorrhage and renal failure, successively. In contrast, in

Asian studies, serious infection was the leading cause of death, followed by renal failure, haemorrhage, malignant tumours and thrombosis, successively (Yu et al 2016).

Important co-morbidities:

- Bone marrow abnormalities.

2.1.2 Atypical haemolytic uraemic syndrome

Incidence and prevalence:

Atypical haemolytic uraemic syndrome (aHUS) is a rare disorder. The estimated annual incidence of aHUS in the US is approximately 1 to 2 cases per million (Constantinescu et al 2004). The estimate for Europe is similar at 1.5-1.8 cases per million population (Salvadori and Bertoni 2013).

A chart review study from Italy (2003-2012) found an average annual incidence of 0.75 cases per million children (age below 18 years) (Ardissino et al 2016) and another chart review study from Norway (1998-2008) found an average annual incidence of aHUS (defined as diarrhoea-negative HUS) to be <0.1 per 100,000 children (age<16 years) (Jenssen et al 2014).

Approximately 40% of patients are diagnosed during childhood (Fremeaux-Bacchi et al 2013, Noris et al 2010, Noris and Remuzzi 2009), with a reported prevalence of aHUS in a paediatric population of 3.3 per million, based on the data from the European HUS registry (Zimmerhackl et al 2006). Furthermore, a chart review study from Italy (2003-2012) found a point prevalence of 9.4 per million children (below 18 years of age) (Ardissino et al 2016).

Demographics of the population in the authorised indication and risk factors for the disease:

aHUS can occur at any age, from the neonatal period to the adult age (extremes: 1 day to 83 years) (Loirat and Frémeaux-Bacchi 2011), but the earliest cases (onset during the first 6 months of life) are suggestive of aHUS (Loirat and Frémeaux-Bacchi 2011). Data suggest that the average age of onset may be significantly lower in aHUS cases compared to HUS patients with diarrhoea (Constantinescu et al 2004, Zimmerhackl et al 2006). The age of onset may differ based on underlying genetics.

In paediatric registries of aHUS, the median age of onset ranges from 25 months to approximately 8 years (Ardissino et al 2016, Constantinescu et al 2004, Dragon-Durey et al 2010, Zimmerhackl et al 2006). In adults, the median age of onset ranges from 36 to 65 years (Fakhouri et al 2016).

In a European paediatric aHUS registry, 56% of patients were male and the mean age of onset among the 167 cases was 25 months, with many cases developing within the first year of life

(Zimmerhackl et al 2006). In a French cohort of 46 paediatric aHUS patients, 56% were male and 70% experienced onset before the age of 2 years (Sellier-Leclerc et al 2007). Similarly, among 27 Canadian children with aHUS (defined as HUS without diarrhoea), 63% were male and the median age of onset was 2 years (Constantinescu et al 2004). In the Northern Italian HUS Network, the median age of onset among paediatric aHUS cases was 3 years and 55% were male (Ardissino et al 2016). In 45 aHUS patients who were also positive for anti-factor H autoantibodies, the median age of onset was 8.5 years among 38 children (66% male) between the ages of 8 months and 14 years; the median age of onset in 7 adults (100% male) between the ages of 28 and 52 was 41 years (Dragon-Durey et al 2010).

In a larger study that includes adult and paediatric patients, the gender distribution was nearly 1:1 (Noris et al 2010), and in a registry that included adult and paediatric aHUS patients in German-speaking Europe, 40% of identified cases were male and the mean age at diagnosis was 30 years, but this registry only included adults initially before being expanded to children and adolescents (Sullivan et al 2010).

Most aHUS patients in the literature are Caucasians (Constantinescu et al 2004, Dragon-Durey et al 2010, Fakhouri et al 2016, Maga et al 2010, Sellier-Leclerc et al 2007, Westra et al 2010). However, this may be due to the fact that most studies are from Europe and North America. Although specific ratios vary, demographic data on paediatric aHUS shows the predominance of males, whereas among adult aHUS patients, there tends to be a predominance of females (Fremeaux-Bacchi et al 2013, Licht et al 2015, Sheerin et al 2016).

Risk factors:

The most common aHUS-related genetic abnormality is in complement factor H (CFH), affecting approximately 11% to 29% of aHUS cases based on aHUS registry data, followed by member co-factor protein, complement factor I (CFI), and C3, each affecting approximately 2% to 17% of patients, and finally Factor B and thrombomodulin, each affecting approximately 0% to 5% of patients (Maga et al 2010, Salvadori and Bertoni 2013). A similar ranking of the frequency of aHUS-related genetic mutations was found among adult aHUS patients in a Phase 2 trial to assess the efficacy of eculizumab. Overall, 49% of cases had a genetic abnormality: 24% had a CFH mutation, 10% had a C3 mutation, 5% had a CFI, and 5% had a membrane cofactor protein (MCP) mutation (Fakhouri et al 2016). Mutations in the diacylglycerol kinase epsilon gene have also been shown to be associated with development of aHUS and patients with this recessive mutation typically present before 1 year of age, have persistent hypertension, haematuria and proteinuria, and later develop chronic kidney disease (Lemaire et al 2013).

The role of genetic mutations in risk for aHUS may be greater at younger ages: in a cohort of 46 paediatric aHUS cases in France, genetic mutation was associated with younger age of

onset (Sellier-Leclerc et al 2007), and in a German aHUS registry, 20% of cases in patients aged 20 years or less were associated with a known mutation, but only 9% of those over the age 20 (Sullivan et al 2010).

A German aHUS registry estimated that 28% of aHUS cases experienced a recurrence (Sullivan et al 2010). CFH and MCP haplotypes have been shown to increase the likelihood of aHUS recurrence (Noris et al 2010). A genetic study of 45 paediatric aHUS cases in Belgium and the Netherlands, found that those with mutations in complement regulating genes were more likely to experience aHUS relapse (65% relapsed) versus those without a mutation (32% relapsed) (Geerdink et al 2012). A prospective follow-up of 45 aHUS patients who tested positive for anti-factor H autoantibodies observed a 58% recurrence rate, with 68% of relapses occurring within 6 months of initial onset (Dragon-Durey et al 2010).

Fewer than 20% of aHUS cases are believed to be familial (Noris and Remuzzi 2009, Sullivan et al 2010). Of the 732 aHUS patients enrolled in the Alexion-sponsored aHUS registry, approximately 16% had a family history of aHUS (M11-001 2015). A review of aHUS-related genetic abnormalities and clinical outcomes concluded that patients with familial aHUS have poorer prognoses, and that it is associated with an increased risk for relapse (Geerdink et al 2012, Noris and Remuzzi 2009).

Frequently, aHUS is triggered by an infectious event, usually an upper respiratory infection or gastroenteritis. This occurs in approximately 50% of adult cases and 80% of paediatric cases (Loirat and Frémeaux-Bacchi 2011, Salvadori and Bertoni 2013). It was also found that an infectious trigger was more common in those with known MCP mutations versus those with no mutations or with CFH mutation only (Caprioli et al 2006). Pregnancy is a notable trigger for aHUS. Out of 100 female aHUS cases in a retrospective study conducted between 2000 and 2008, 21 were triggered by pregnancy; of these, 18 (86%) had a complement abnormality (Fakhouri et al 2010). The risk of pregnancy-triggered aHUS was highest during second pregnancies and the mean age of onset was younger in pregnancy-related aHUS patients (26 years) than among the women whose aHUS was not pregnancy related (33 years). It is estimated that, among pregnancy-related aHUS, 20% of cases develop during pregnancy and 80% develop during the postpartum period (Salvadori and Bertoni 2013).

The main existing treatment options:

Prior to the introduction of eculizumab, only supportive measures for treatment of aHUS were available, such as transfusions of red blood cells and platelets, dialysis, plasma exchange or plasma infusion and immunosuppression. The role of plasma in this condition is not completely elucidated.

Antibiotics may be used when aHUS is precipitated by an infectious event. Because severe hypertension is common in aHUS, drugs to control blood pressure may be needed (Kavanagh et al 2006).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Up to 25% of aHUS patients may die in the acute phase of the disease and approximately 50% may require ongoing renal replacement therapy (Kavanagh et al 2006, Rafiq et al 2015). However, although the course of aHUS can indeed be life-threatening, there is a wide range of clinical outcomes within aHUS and some patients have only mild disease while others progress to severe outcomes or death (Kavanagh et al 2006).

The onset of aHUS is typically sudden, and children may typically present with symptoms including pallor, general distress, vomiting, loss of appetite, and fatigue while adults more typically present with fatigue and general distress. Upon clinical investigation, most patients demonstrate the three hallmark symptoms defining HUS, including haemolytic anaemia, thrombocytopenia and renal impairment. However, when diagnosis is delayed, patients may progress to more severe symptoms, including hyperkalaemia, acidosis, and volume overload with arterial hypertension and hyponatraemia. More than a half of patients typically receive dialysis at diagnosis and approximately 20% of patients have extra-renal complications with neurologic complications being the most frequent (Loirat and Frémeaux-Bacchi 2011).

In a retrospective paediatric cohort study conducted in Northern Italy between 2003 and 2012, one out of 12 cases of aHUS died, due to sepsis, for a case fatality rate of approximately 8% (Ardissino et al 2016). Another Italian study identified 9 cases of aHUS (defined as HUS without diarrhoea): five of those cases had a recurrence, one of whom died during a combined kidney-liver transplant surgery (Micheletti et al 2010). Four patients (9%) in a Dutch and Belgian paediatric cohort of 45 aHUS patients died, one during the acute phase of the disease and three others later (Geerdink et al 2012). The long-term (average of 39 months) follow-up of 45 international aHUS patients who were positive for anti-factor H autoantibodies, revealed that 4 (9%) patients had died. Two deaths were in children and the causes were pulmonary hypertension and unexplained (following a dialysis session). The other two deaths were among adults, one from cardiac insufficiency and the other from an unknown cause (Dragon-Durey et al 2010). Finally, in a French cohort of 46 aHUS patients, 4 died within a few weeks or months of symptom onset, and within a year 37% had either died or developed end-stage renal disease (ESRD; (Sellier-Leclerc et al 2007).

The risk of death from aHUS is greatly increased among those with CFH mutations.
A case-control study that included patients from the International Registry of Recurrent and Familial HUS/thrombotic thrombocytopenic purpura found a statistically significant association between CFH mutation and death. In this study, 5% of patients with no mutations

died following their first episode and 30% of patients with a CFH mutations died following their first episode. This same pattern continued upon long-term follow-up (Caprioli et al 2006). A more recent analysis of the same registry showed that, in addition to CFH mutation, a thrombomodulin irregularity is also associated with an increased risk of death. Upon their first aHUS episode, 19% and 31% of patients with CFH and thrombomodulin mutations died and this pattern held for at least three years. The authors noted that patients with familial aHUS tend to have a poor prognosis, with 50% to 80% progressing to ESRD or death (Noris et al 2010, Noris and Remuzzi 2009). One study noted that increased creatinine level at first aHUS episode is significantly correlated with the risk for ESRD or death during the first year (Sellier-Leclerc et al 2007).

Important co-morbidities:

- Renal disease.
- Arterial hypertension.
- Central nervous system disease.
- Cardiovascular disease.
- Autoimmune disease.

2.1.3 Anti-acetylcholine receptor antibody-positive generalised myasthenia gravis

Incidence and prevalence:

Myasthenia gravis (MG) is a rare chronic autoimmune disorder that can lead to symptoms of varying severity such as difficulty chewing or swallowing, muscle weakness, and difficulty breathing. The majority of the prevalent cases are generalised MG (gMG).

A systematic review focused on 31 primarily European studies published between 1980 and 2007, estimated that the annual incidence of MG is approximately 30 per million persons. The authors found increased incidence over time and suggested that prospective studies, which found incidences ranging from 20 to 30 per million per year, may be most accurate (McGrogan et al 2010). Similarly, a recent study conducted among the national registers in Sweden reported an annual incidence of 29 per million in 2016 (Westerberg and Punga 2020).

While a wide range of prevalence estimates have been reported in several epidemiological studies, a recent and robust study based in Sweden identified cases with a primary or secondary diagnosis of MG or two or more prescriptions of pyridostigmine or ambenonium and reported a prevalence of 361 patients per million (Westerberg and Punga 2020).

About 75% of diagnosed prevalent cases of MG reported in European studies are gMG (Fang et al 2015, Joensen 2014, Lefter et al 2017, Pallaver et al 2011, Santos et al 2016). The most

frequently found autoantibodies among patients with gMG are directed against acetylcholine receptor (AChR) and muscle-specific kinase (MuSK). About 70% to 88% of patients with gMG are AChR antibody positive, and 7% to 12% are MuSK antibody positive (Anil et al 2020, Hendricks et al 2019, Oh 2009, Tomschik et al 2020).

Demographics of the population in the authorised indication and risk factors for the disease:

As the incidence of MG typically increases with age, and mortality due to MG itself is low, the highest disease prevalence is observed in the older age group (Carr et al 2010). Most studies show MG incidence increasing for men in the 60- to 80-year-old age group. However, the incidence of MG generally has a bimodal age distribution in women with a peak in the 20- to 40-year-old age group and then again in the 50- to 70-year-old age group (Carr et al 2010, McGrogan et al 2010).

Risk factors:

Most studies suggest that MG incidence and prevalence increase with age, although there is some variation by study (Gattellari et al 2012, McGrogan et al 2010). In a population-based study using the Taiwan National Health Insurance Research Database, a family history of systemic lupus erythematosus was found to be associated with an increased risk of MG with a relative risk of 2.95 (95% CI: 2.04, 4.26) after adjustment for age, sex, place of residence, income, occupation, and family size (Kuo et al 2015). Another study in this database found that risk of MG was elevated in patients with allergic conjunctivitis, allergic rhinitis, Hashimoto's thyroiditis, Graves' disease, and diabetes mellitus (Yeh et al 2015). In a meta-analysis, some polymorphisms in the human leukocyte antigen (*HLA*)-DRB1 gene were found to be associated with increased risk of late-onset MG. Specifically, DRB1 07 and DRB 0403 alleles were associated with increased risks of 1.83 (95% CI: 1.12, 2.98) and 7.05 (95% CI: 2.62, 18.92), respectively (Ling et al 2020). Thymomas are also a risk factor with about 30% of patients with thymoma developing MG (Marx et al 2013).

The main existing treatment options:

As with other chronic, disabling immune-mediated diseases, the goal of treatment for gMG is to achieve and maintain the absence or minimal presence of clinical signs and symptoms.

The current recommended treatment paradigm starts with a trial of standard immunosuppressant therapies or immunomodulatory therapies based on the International Consensus Guidance for Management of Myasthenia Gravis (Narayanaswami et al 2021). Current standard of care for gMG includes treatment with acetylcholinesterase inhibitors, immunomodulatory therapies (immunosuppressant therapies, corticosteroids, nonsteroidal immunosuppressive treatments, intravenous immunoglobulin, and plasmapheresis/plasma

exchange), surgical immunomodulatory treatment (thymectomy), and anti-C5 treatment with eculizumab.

Most gMG patients start with symptomatic treatment with acetylcholinesterase inhibitors, but in a considerable proportion, corticosteroids and/or immunosuppressant therapies become necessary while intravenous immunoglobulin and plasmapheresis/plasma exchange are mostly used as rescue therapies in cases of clinical deterioration (Mantegazza et al 2020). Corticosteroids are effective in a majority of patients with gMG as chronic treatments; however, neurologists seek to use the minimal effective dose since patients are treated for very long periods and chronic steroid use can be associated with long-term adverse effects (Mantegazza et al 2020, Menon et al 2020). Approximately 10% to 15% of patients with gMG fail to respond adequately to, or cannot tolerate multiple therapies for gMG and continue to suffer profound muscle weakness and severe disease symptoms that limit everyday function (Huda et al 2014, Silvestri and Wolfe 2014).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Muscle weakness is the primary sign and symptom of gMG (Gilhus and Verschuuren 2015, Meriggioli and Sanders 2009). Patients with gMG commonly present with ocular symptoms and progress to generalised weakness within 2 years of disease onset. Facial and bulbar weakness are common in gMG. Weakness can also extend to limb-girdle and respiratory muscles. The involvement of respiratory muscles can be life-threatening and require immediate intervention. The course of gMG varies by patient, and most patients experience at least one exacerbation of their symptoms, which can be triggered by certain stressors (eg, some medications, infection, surgery, emotional stress) (Hehir and Silvestri 2018, Meriggioli and Sanders 2009). Additionally, 15% to 20% of patients with gMG experience a myasthenic crisis, usually within 3 years of diagnosis (Hehir and Silvestri 2018). Remission may occur in 10% to 20% of patients (Grob et al 2008).

Hospitalisations for gMG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (eg, during myasthenic crisis), with no substantial improvement in length of hospitalisation or in-hospital mortality from 1991-1992 to 2001-2002 (Souayah et al 2009).

Patients with gMG that have remaining symptomatology are likely to have diminished work capacity, difficulty caring for themselves and for others, and require assistance in their activities of daily living including driving, eating, grooming or household chores (Boscoe et al 2019, Harris et al 2019).

Mortality in gMG has decreased steadily from 1940 through 2000 due to improved treatment and respiratory intensive care (Grob et al 2008). Most recently, a mortality rate of 1.51 per

100 patients has been reported among Swedish patients with gMG enrolled in the Swedish National Patient Register from 2006 to 2016, which is comparable to the Swedish general population (Westerberg and Punga 2020). Similarly, a retrospective study conducted in Austria using medical records of patients with gMG from 2000 to 2018 reported that the observed mortality rate among the gMG patients in the study was consistent with the general population (Tomschik et al 2020).

Important co-morbidities:

- Diabetes mellitus.
- Other autoimmune disease (eg, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis).
- Malignancy.
- Infection.
- Dyslipidaemia.
- Depression.

2.1.4 Neuromyelitis optica spectrum disorder in patients who are anti-aquaporin 4 antibody positive

Incidence and prevalence:

Neuromyelitis optica spectrum disorder (NMOSD) is a rare disease worldwide and the published estimates of incidence and prevalence vary widely among different geographic areas and ethnicities, only partially explained by different study methods and disease definitions (Papp et al 2021). Differences based on geographic location remain unclear (Holroyd et al 2020).

Current prevalence estimates range from 0.7 to 10 per 100,000 population, depending on the population (Holroyd et al 2020). In a systematic review of the worldwide epidemiology of NMOSD, published incidence estimates ranged between 0.039 and 0.73 per 100,000 person-years for adults (Papp et al 2021). The highest estimated incidence and prevalence of NMOSD were found in the Afro-Caribbean region, while the lowest estimated incidence and prevalence were found in Australia and New Zealand (Papp et al 2021).

European population-based studies provided estimated prevalence ranging from 1.91 to 4.4 per 100,000 population and incidence ranging from 0.1 to 0.4 per 100,000 population (Asgari et al 2011, Cossburn et al 2012, Papp et al 2020).

More than 60% of European patients with NMOSD had antibodies against AQP4 (Asgari et al 2011, Cossburn et al 2012, Hamid et al 2017, Papp et al 2020). The percentage of AQP4 antibody seropositivity ranged from 60% to 90% in epidemiologic literature (Papp et al 2021).

Demographics of the population in the authorised indication and risk factors for the disease:

NMOSD is more common in women than in men, with an average age at onset typically between 30 and 40 years (Holroyd et al 2020, Papp et al 2020). The mean age at onset varied in studies from 29.2 to 45.7 years, whereas the median age was between 30.5 and 43 years (Papp et al 2021).

Women were also more likely to be AQP4 antibody seropositive than men (Borisow et al 2016, Jarius et al 2012).

NMOSD varies by race/ethnicity, being more common in people with African and Asian ancestries who have a disproportionately greater risk to develop NMOSD compared with White ethnic groups (Bukhari et al 2017, Flanagan et al 2016, Papp et al 2021).

Risk factors:

The environmental risk factors for NMOSD remain unclear, though there may be increased risk with low fruit and vegetable consumption, low physical activity, smoking, and low levels of vitamin D (Holroyd et al 2020).

As shown above, race and female gender represent potential risk factors for NMOSD. Although infections are believed to play a role in some autoimmune diseases, a role in NMOSD is unclear.

Clustering of NMOSD has also been seen in families (in approximately 3% of NMOSD cases). A recent whole-genome sequence study identified genetic variants that may be linked to NMOSD including a structural variation in C4a and C4b complement copy numbers similar to variants in lupus patients. Finally, it remains well established that those with existing autoimmune conditions, such as lupus, myasthenia gravis, and Sjögren’s syndrome, are at higher risk of developing NMOSD (Holroyd et al 2020, Papp et al 2021).

Risk factors for relapse of NMOSD are varied. In a multicentre study of 175 Caucasian patients in Germany with NMOSD identified between August 2009 and August 2011, relapse was more common in patients who were AQP4 antibody seropositive than in patients who were seronegative (92.7% versus 72.6%) (Jarius et al 2012). In a study of 127 German patients, each decade of age was associated with a lower risk of relapses, while a previous relapse on the same treatment tended to be associated with future relapses (Stellmann et al 2017).

The main existing treatment options:

Prior to approval of eculizumab (SOLIRIS) as a treatment for NMOSD, treatment consisted of corticosteroids and non-specific immunosuppressive therapies, including azathioprine,

rituximab, mycophenolate mofetil, methotrexate, and mitoxantrone. The use of these medications was based on clinical experience and consensus (Trebst et al 2014). However, despite these therapies, a significant number of patients (> 50%) continue to have relapses, resulting in additional and permanent neurologic deficits and disability (Bichuetti et al 2015, Bichuetti et al 2010, Costanzi et al 2011, Kim et al 2011, Mealy et al 2014, Poupart et al 2020, Royston et al 2021, Stellmann et al 2017).

The primary treatment for an NMOSD attack is high-dose intravenous methylprednisolone, which is followed in some cases by a steroid tapering for 2 weeks to 2 months after initial treatment. Plasma exchange is also recommended if steroids are not successful in controlling the symptoms and for complex cases, cyclophosphamide has been added to the regimen. For prevention of relapses, as noted above, immunosuppressive treatments include azathioprine, rituximab, mycophenolate mofetil, methotrexate, oral corticosteroids, and mitoxantrone (Kimbrough et al 2012, Sherman and Han 2015).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Relapse is common in NMOSD and recurrent disease was reported in 85.2% to 94% of patients with NMOSD (Jarius et al 2012, Kitley et al 2014, Kleiter et al 2016). In a retrospective multicentre study of 175 Caucasian patients in Germany with NMOSD identified between August 2009 and August 2011, patients relapsed 5 times on average over an average disease course of 57.5 months, with 92.7% of the AQP4 antibody seropositive patients experiencing at least one relapse (Jarius et al 2012).

Mortality in NMOSD is a significant risk following diagnosis and morbidity is significant and may include visual disabilities and/or motor disabilities during attacks, and some patients may experience extended or permanent disability (Kitley et al 2014).

In a study of the clinical outcomes of 106 consecutively enrolled AQP4 antibody seropositive NMOSD patients in the United Kingdom and Japan between 2006 and 2010, 10 patients (9.4%) died after a median disease duration of 99 months, and 7 of 10 deaths were directly attributable to NMOSD or complications of NMOSD. The mean age at death in this population was 52 years and older age was strongly predictive of death, but gender, onset attack severity and type of onset attack were not associated with death. Further, morbidity was significant with 18% experiencing permanent visual disability, 34% experiencing permanent motor disability, and 23% experiencing wheelchair dependency during the follow-up period. Of the 86 patients who experienced a relapse, 62% had attacks of optic neuritis as well as longitudinally extensive transverse myelitis (LETM), 18% had only LETM, and 9% had relapsing optic neuritis (Kitley et al 2014).

Based on data from a multicentre study of 9 sites across the world of 258 patients with NMOSD, brainstem symptoms were reported in 81 patients (31.4%) and occurred more commonly in a non-Caucasian population ($p<0.05$). The most frequently reported brainstem symptoms included uncontrolled vomiting and intractable hiccups (Kremer et al 2014).

Important co-morbidities:

- Infection.
- Severe pain.
- Neurological complications (vision loss, sensory and motor impairment, ambulation difficulties, neurogenic bowel/bladder).

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

Early non-clinical development programme with ravulizumab showed that ravulizumab does not exhibit any pharmacological activity in non-human species.

The absence of product specific nonclinical safety studies is not uncommon for humanised monoclonal antibodies, which do not cross react with the target in commonly used toxicology species.

Thus, in order to study the potential toxicity of long-term inhibition of C5, and to evaluate the influence of such inhibition on reproductive function in mice, a surrogate murine anti-mouse C5 antibody (BB5.1) model was used instead (same murine surrogate was used in the nonclinical testing of eculizumab). Similar to ravulizumab, the BB5.1 surrogate antibody binds directly to and prevents the cleavage of C5, thereby, inhibiting generation of both C5a and C5b 9 in the mouse.

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

A 26-week toxicity study performed with BB5.1 provided the no-observed-effect level (NOEL) at 60 mg/kg/week.

Reproductive/developmental toxicity

Reproductive toxicity studies carried out in male and female mice demonstrated a no-observed-adverse-effect level for male toxicity of 60 mg/kg/week, while the NOEL for female toxicity, male and female fertility, and embryo-foetal viability was 60 mg/kg/week or greater.

2.2.2 Other toxicity-related information or data

Tissue cross-reactivity studies

These studies described the binding profile of ravulizumab in a standard human tissue set and limited non-specific binding in cynomolgus monkey tissues. In the human tissue set, most of the binding observed was cytoplasmic in nature, and it is unlikely that the cytoplasm and cytoplasmic structures would be accessible to ravulizumab *in vivo*. The differences in binding between the human and monkey tissue sets further support the assertion that cynomolgus monkeys were not a relevant toxicology species.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

This section summarises exposure data from the clinical development programmes for ravulizumab. The overall cumulative exposure to ravulizumab (by indication) is provided in Table 2-1.

Table 2-1 Cumulative clinical trial exposure to ravulizumab

Exposure by indication	Patients (N)	Person time (patient-years)
aHUS	92	210.78
gMG	169	342.05
NMOSD	58	154.38
PNH	488	1,713.38

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria.
Final study data for PNH, aHUS and gMG studies that includes ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, ALXN1210-PNH-302, ALXN1210-PNH-304, ALXN1210-aHUS-311, ALXN1210-aHUS-312 and ALXN1210-MG-306. Interim analysis data for NMOSD study ALXN1210-NMO-307 (16 June 2023).

Table 2-2 Age group and sex

Age group	Patients (N)		Person time (patient-years)	
	M	F	M	F
All indications combined				
28 days to <24 months	3	4	4.45	0.76
24 months to <12 years	10	9	23.88	28.28
12 to <18 years	11	10	30.76	25.36
18 to 65 years	290	342	969.21	1041.39
>65 years	74	54	174.78	121.73
Total	388	419	1,203.08	1,217.51
aHUS				
28 days to <24 months	3	4	4.45	0.76
24 months to <12 years	10	7	23.88	20.50
12 to <18 years	6	4	15.13	9.52
18 to 65 years	16	33	42.96	82.54
>65 years	3	6	2.44	8.62
Total	38	54	88.85	121.93
gMG				
18 to 65 years	46	69	93.41	145.37
>65 years	37	17	71.98	31.28

Table 2-2 Age group and sex

Age group	Patients (N)		Person time (patient-years)	
	M	**F**	**M**	**F**
Total	83	86	165.39	176.65
NMOSD				
18 to 65 years	4	49	10.68	130.74
>65 years	2	3	5.27	7.69
Total	6	52	15.95	138.43
PNH				
24 months to <12 years	0	2	0	7.79
12 to <18 years	5	6	15.63	15.84
18 to 65 years	224	191	822.16	682.73
>65 years	32	28	95.10	74.14
Total	261	227	932.88	780.50

aHUS, atypical haemolytic uraemic syndrome; F, female; gMG, generalised myasthenia gravis; M, male; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria.
Final study data for PNH, aHUS and gMG studies that includes ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, ALXN1210-PNH-302, ALXN1210-PNH-304, ALXN1210-aHUS-311, ALXN1210-aHUS-312 and ALXN1210-MG-306. Interim analysis data for NMOSD study ALXN1210-NMO-307 (16 June 2023).

Table 2-3 Race

Race	Patients (N)	Person time (patient-years)
All indications combined		
White	425	1,179.79
Black or African American	34	96.24
American Indian or Alaska Native	4	10.00
Asian	265	838.06
Other	17	64.56
Unknown	9	28.75
Not reported	53	203.18
Total	807	2,420.59
aHUS		
White	47	102.76
Black or African American	6	14.72
American Indian or Alaska Native	1	2.81

Table 2-3 Race

Race	Patients (N)	Person time (patient-years)
Asian	27	60.44
Other	2	6.21
Unknown	2	5.13
Not reported	7	18.72
Total	92	210.78
gMG		
White	124	246.44
Black or African American	6	13.17
American Indian or Alaska Native	1	2.63
Asian	29	63.27
Other	1	1.57
Unknown	1	2.03
Not reported	7	12.92
Total	169	342.05
NMOSD		
White	29	74.28
Black or African American	6	18.38
Asian	21	55.49
Unknown	2	6.23
Total	58	154.38
PNH		
White	225	756.32
Black or African American	16	49.97
American Indian or Alaska Native	2	4.56
Asian	188	658.87
Other	14	56.77
Unknown	4	15.35
Not reported	39	171.54
Total	488	1,713.38

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria. Final study data for PNH, aHUS and gMG studies that includes ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, ALXN1210-PNH-302, ALXN1210-PNH-304, ALXN1210-aHUS-311, ALXN1210-aHUS-312 and ALXN1210-MG-306. Interim analysis data for NMOSD study ALXN1210-NMO-307 (16 June 2023).

2.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Unresolved meningococcal infection

Reason for exclusion: Based on ravulizumab mode of action (ie, inhibition of terminal complement), patients are more vulnerable to infections, especially those caused by *Neisseria meningitidis*.

Is it considered to be included as missing information: No

Rationale: The use of ULTOMIRIS is contraindicated in patients with unresolved meningococcal infection. Moreover, all patients eligible for ULTOMIRIS must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W 135, and B) where locally available and/or be on prophylactic antibiotics until 2 weeks after vaccination as per local guidelines.

Pregnancy and breast-feeding

Reason for exclusion: The main reason was ethical since no developmental/reproductive toxicity studies with ravulizumab were conducted. The studies with a surrogate murine BB5.1 did not show any signs of reproductive or developmental toxicity in the preclinical development programme.

Is it considered to be included as missing information: Yes

Rationale: Not applicable.

Presence of an active and untreated (systemic) infection

Reason for exclusion: Undiagnosed complement-mediated diseases or other underlying aetiology for active systemic infections may increase risk of infection or may confound clinical assessment of ravulizumab.

Is it considered to be included as missing information: No

Rationale: Patients who developed non-neisserial infection within the study were not automatically discontinued from the study. Therefore, data on use of ravulizumab during infection has been collected.

ULTOMIRIS is intended for long-term therapy. Therefore, in the clinical practice, it is not advisable to interrupt the use of ravulizumab in the presence of an active infection, as patients

benefit from the long-term effects of ravulizumab and treatment interruption may trigger worsening of PNH or aHUS, gMG, or NMOSD.

Post-transplant patients (solid organ transplant other than kidney patients and bone marrow transplant/haematopoietic stem cell transplant patients)

Reason for exclusion: Underlying amplified complement condition may confound clinical assessment of ravulizumab and may have different pharmacokinetic/pharmacodynamic effects.

Is it considered to be included as missing information: No

Rationale: The benefit-risk profile of ravulizumab in patients who underwent solid organ or bone marrow transplant/haematopoietic stem cell transplant is not expected to differ from the profile seen in patients with aHUS, who were included in the clinical development programme.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reaction, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breast-feeding women	Not included in the clinical development programme.
Elderly patients	Patients of different age groups were included within the clinical development programme. Refer to Table 2-2.
Patients with relevant comorbidities:	
• Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	The specific data on exposure in PNH, gMG, and NMOSD patients with specific comorbidities are not available. The development programme in patients with complement-mediated TMA, including aHUS included patients with impaired renal function. No other co-morbidities were specifically investigated.
Population with different race/ethnic origin	Patients with different race were included in the clinical development programme. Refer to Table 2-3.
Subpopulations carrying relevant genetic polymorphism	Not included in the clinical development programme.

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria; TMA, thrombotic microangiopathy.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

Alexion has been collecting information on the number of patients on treatment since the commercial launch date of ravulizumab. Exposure was estimated for each quarter starting with the first quarter of 2019, based on aggregate US commercial data since it was initially launched in the US. Beginning with July 2019, exposure was estimated monthly. Although the International Birth Date (IBD) is 21 December 2018, there were no commercial patients until January 2019. It is to be noted that sales were initially only in the US, sales in Europe began in July 2019, sales in the Japan and Asia-Pacific region began in October 2019 and sales in the Latin America region began in September 2021.

Patients were considered new to treatment, continuing, or discontinued from treatment. The number of new patients and patients who permanently stopped treatment were provided from Alexion's commercial database. The number of continuing patients in a quarter (or a month) was determined as the difference between the number of patients on treatment at the end of the previous quarter (or a month) and discontinued patients in the current quarter (or a month). To simplify the calculation, Alexion assumed that there is no discontinuation among new patients who started treatment in a given quarter (or a month).

A quarter is 3 months in duration, and continuing patients were assigned the full 3 months of exposure. As for new and discontinued patients, some patients will have more than 1.5 months of exposure, and some will have less than 1.5 months. As such, new and discontinued patients were assigned 1.5 months of exposure time for a quarter. For monthly timeframes, the aforementioned methodology was similarly applied. New and discontinued patients were assigned 0.5 month for each month exposed, and continuing patients were assigned one month for each month exposed.

Patient-months were converted into patient-years by dividing by 12. The total patient-years of exposure for each quarter were calculated by adding the patient-years of exposure for new, continuing, and discontinued patients for the given quarter. The cumulative patient-year exposure was calculated by adding the exposure from the given quarter to that of each previous quarter.

Commercial data are only available for patients in the US. Therefore, in order to estimate patient exposure for regions outside of the US, data that Alexion maintains on vials of product manufactured and distributed were used for exposure estimations. Specifically, the number of new patients and patient-year exposure in regions outside of the US, where patient-level commercial data are not available, were estimated by applying the ratio of product

manufactured and distributed by region to the available US patient-level commercial data and calculated estimates. Actual vial data were used for each month in which an average was used.

To estimate post-marketing exposure over the 12-month interval period of this report and cumulatively from the IBD, exposure estimates for the different periods were summed.

The data provided are estimates based on a series of widely used epidemiologic calculation techniques. Regions or groups with smaller case numbers are particularly prone to perceived "fluctuations" due to the estimation assumptions and data rounding. The most recent data should be regarded as the most accurate representation.

2.5.1.2 Exposure

Table 2-5 provides the estimated number of new patients and patient-years by region, exposed to ULTOMIRIS cumulatively from the IBD through 30 June 2024.

Table 2-5 Estimated cumulative post-marketing exposure to ULTOMIRIS by region

Region	Number of patients	Person time (patient-years)
EMEAC	4,394	8,149
JAPAC	3,607	6,516
LATAM	57	93
CCI [redacted]	7,801	12,929
Total	**15,859**	**27,686**

EMEAC, Europe, Middle East, Africa, and Canada; JAPAC, Japan and Asia-Pacific; LATAM, Latin America.

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for misuse of ravulizumab for illegal purposes is considered negligible, given the characteristics of the drug.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks:

– **Meningococcal infection**

Risk-benefit impact:

Deficiency of terminal complement is associated with an increased incidence of infections caused by *Neisseria* spp., especially *N meningitidis*. Meningococcal infections represent serious, life-threatening conditions, especially if not recognised in a timely manner and treated with appropriate antibiotics. Meningococcal infections can present as sepsis or as meningitis. In the ravulizumab clinical trials, the meningococcal infections presented as sepsis. Increased risk of meningococcal infections is directly associated with the ravulizumab mode of action, causing deficiency in terminal complement components.

Important potential risks:

– **Serious haemolysis after drug discontinuation in PNH patients**

Risk-benefit impact:

This potential risk is based on a theoretical possibility, associated with abrupt ULTOMIRIS discontinuation, resulting in a so-called rebound effect. Rebound effect is described for many biologicals but has not yet been observed with either ravulizumab or eculizumab.

– **Immunogenicity**

Risk-benefit impact:

Potential immunogenicity is common to all biologics. Patients may develop “asymptomatic” antidrug antibodies (ADA) which do not cause either loss of efficacy or any adverse drug reactions, or they may develop neutralising antibodies, known to cause a variable level of loss of drug’s efficacy. Treatment-emergent ADA-positive samples identified in the healthy volunteers or PNH patients have not been linked to any adverse clinical outcome.

Patients may, in general, also develop neutralising antibodies or antibodies leading to serious adverse reactions (mostly allergic/hypersensitivity reactions in nature). Neither of these effects

have been observed in the clinical development programme for ravulizumab. No clinically meaningful outcomes resulting from the development of anti-ravulizumab ADA were described in the ravulizumab clinical trials.

– **Serious infections**

Risk-benefit impact:

Ravulizumab is an inhibitor of the terminal complement. However, since early complement components are not inhibited, the role of ravulizumab in patients' susceptibility to infections other than those caused by *Neisseria* spp. should be minimal. The mechanism which may lead to serious infections other than caused by *Neisseria* spp. in patients treated with ravulizumab/eculizumab remains unclear. PNH patients receiving ravulizumab are often at increased risk of infection due to the underlying medical condition or its complications. Considering the mode of ravulizumab action and the currently missing evidence, serious infections in PNH patients represent a potential risk of ULTOMIRIS.

– **Malignancies and haematologic abnormalities in PNH patients**

Risk-benefit impact:

The natural evolution of the PNH disease makes PNH patients more prone to development of haematologic abnormalities or malignancies as approximately 30% to 70% of PNH patients eventually develop aplastic anaemia or myelodysplastic syndrome (de Latour et al 2008, Hillmen et al 1995, Socié et al 1996). The potential role of ravulizumab in such abnormalities or malignancies (if any) is unknown.

Missing information:

– **Use in pregnant and breast-feeding women**

Risk-benefit impact:

There are no human data on the use of ravulizumab during pregnancy and breast-feeding. Some immunoglobulins are known to cross placental barrier and be likely excreted into the breast milk. However, ravulizumab immunoglobulin G (IgG) 4 heavy chain sequences were combined to form a hybrid constant region that is unable to bind Fc receptors which is a prerequisite to actively cross the placental barrier. Considering the ravulizumab mode of action and the missing data, the benefit-risk balance of ULTOMIRIS remains currently unknown in these patient populations.

2.7.2 New safety concerns and reclassification with an updated RMP

Not applicable.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

2.7.3.1.1 Important identified risk 1: Meningococcal infection

Potential mechanisms:

Complement is known to play an important role in host defence against infections (Ram et al 2010). Deficiency of terminal complement is associated with an increased incidence of infections caused by *Neisseria* spp., especially *N meningitidis*. The increased susceptibility to infections caused by *N meningitidis* is directly related to the ravulizumab mode of action (inhibition of C5), resulting in deficiency of terminal complement components.

Evidence source(s) and strength of evidence:

This important identified risk is based on the ravulizumab mode of action, findings from the clinical trial development programme for ravulizumab, post-marketing experience with ravulizumab and on the long-term experience with eculizumab (SOLIRIS).

The link between terminal complement components deficiency states and (serious) infections caused by *N meningitidis* is firmly established and evidenced by the scientific literature (Figueroa and Densen 1991, Ram et al 2010, Ross and Densen 1984).

Characterisation of the risk:

As of the data lock point of 30 June 2024, a total of 34 meningococcal cases were reported, of which 28 cases originated from the post-marketing experience and 6 from the clinical trials (ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, and ALXN1210-NMO-307).

The cumulative incidence rate for meningococcal infections in clinical trial setting is approximately 0.18 cases per 100 patient-years (6 cases per 3,264.2 patient-years) since the Development IBD (DIBD) for ravulizumab until 30 June 2024 (in all investigated therapeutic areas).

As of 30 June 2024, the cumulatively post-marketing rate for meningococcal infections is approximately 0.10 cases per 100 patient-years (28 cases per 27,685.8 patient-years).

Meningococcal infections are life-threatening conditions with potentially fatal outcomes if not promptly diagnosed and treated. Timely diagnosis and treatment initiation immediately after infections presentation showed to markedly impact the outcome (Vyse et al 2013). The

majority of affected patients to date recovered after initiation of appropriate treatment, consisting of antibiotics (intravenously or orally administered ceftriaxone).

In general, meningococcal infections may leave patients with disabling permanent sequelae including physical, neurological, cognitive, behavioural and psychological consequences such as hearing loss, amputations, spasticity, skin scarring, seizures, and neurodevelopmental deficits (Pace and Pollard 2012, Vyse et al 2013).

Risk factors and risk groups:

Main risk factors for these infections include:

- Genetic deficiency or therapeutic inhibition of terminal complement.
- Lack of commercially available vaccine against certain meningococcus serogroup.
- (Partial) resistance of meningococcal strain to prophylactic antibiotics.
- Professionals who are exposed to environments of greater risk for meningococcal disease.
- Research, industrial, and clinical laboratory personnel who are routinely exposed to N meningitidis.
- Military personnel during recruit training (military personnel may be at increased risk of meningococcal infections when accommodated in close quarters).
- Day-care centre workers.
- Living on a college or university campus.
- Travelling to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj).

Preventability:

Ravulizumab must not be initiated in patients with unresolved *N meningitidis* infection or in patients who are not currently vaccinated against *N meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

The occurrence of meningococcal infections can be reduced by means of meningococcal vaccination prior to initiation of ravulizumab treatment. However, vaccines are not available against all known serotypes of *N meningitidis* and not all vaccines are available globally. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Refer to Section 5.2 for a detailed description of additional risk minimisation measures in place, designed to prevent or minimise this risk.

Impact on the risk-benefit balance of the product:

Meningococcal infection is a serious, life-threatening acute condition with potentially fatal outcomes if not recognised in a timely manner and treated. If no preventive measures were established, the impact of this risk on the benefit-risk balance of the product would have been highly unfavourable.

Increased risk of meningococcal infections is directly associated with the ravulizumab mode of action, causing deficiency in terminal complement components, and is, therefore, associated with ULTOMIRIS, with potential impact on the drug's benefit-risk balance.

However, the long-term post-marketing experience with eculizumab showed low and stable overall reporting rates of meningococcal infections in eculizumab-treated patients over the past 16 years (0.24-0.5 per 100 patient-years). Fatalities within eculizumab-treated meningococcal cases occurred at a proportion similar to that reported among meningococcal cases in the general population (MacNeil et al 2018, van Deuren et al 2000). The risk minimisation measures in place to date for the risk of meningococcal infections appear to be appropriate and effective. Identical risk minimisation measures are in place for SOLIRIS (eculizumab) as well.

In the light of this, the anticipated benefits of treatment with ULTOMIRIS outweigh any risks posed by increased susceptibility to meningococcal infections.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.2 Important potential risk 1: Serious haemolysis after drug discontinuation in PNH patients

Potential mechanisms:

Patients with PNH experience chronic haemolysis of terminal complement inhibitor deficient red blood cells also referred to as PNH red blood cells. To the extent that ravulizumab effectively prevents lysis of these cells, the PNH red blood cells may become a higher proportion of the red blood cell population with ravulizumab treatment.

Therefore, PNH patients treated with ravulizumab for a period long enough to increase their number of PNH red blood cells are potentially at risk for serious haemolysis following discontinuation of ravulizumab therapy.

Evidence source(s) and strength of evidence:

This is a theoretical possibility, based on the mode of action of ravulizumab, nature of PNH, and experience with the use (and discontinuation) of SOLIRIS (eculizumab).

Characterisation of the risk:

In clinical studies, there have been no cases that meet the definition of serious haemolysis after discontinuation in patients with PNH either following ravulizumab treatment.

As of the data lock point of 30 June 2024, there have been no cases in post-authorisation experience that met the definition of serious haemolysis after discontinuation in patients with PNH.

Risk factors and risk groups:

No risk factors have yet been identified.

Preventability:

The effects are most likely not completely preventable, but their severity can be minimised by avoiding abrupt drug discontinuation. Close monitoring of patients who discontinue the drug is recommended.

Impact on the risk-benefit balance of the product:

This potential risk is based on the theoretical possibility, associated with abrupt drug discontinuation, resulting in a so-called rebound effect. Rebound effect is described for many biologicals but has not yet been observed with either ravulizumab or eculizumab. Considering the potential impact on the target population, the anticipated benefits of treatment with ULTOMIRIS outweighs any risks.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.3 Important potential risk 2: Severe TMA complications in aHUS patients after ravulizumab discontinuation

Potential mechanisms:

aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Ravulizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of ravulizumab can result in the recurrence complement-mediated thrombotic microangiopathy (TMA), which would result in the appearance of signs and symptoms of severe TMA complications.

Evidence source(s) and strength of evidence:

This potential risk is based on the long-term observational prospective study with eculizumab (Study C11-003). Discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study with eculizumab indicate that patients who discontinued eculizumab experienced a higher rate of TMA recurrence (13.5-fold) and showed a trend toward reduced renal function compared to patients who continued eculizumab treatment (Menne et al 2019).

No such effects have been observed in the clinical development programme for ravulizumab in aHUS patients. However, because of similar mechanism of action, this represents a potential risk for ULTOMIRIS.

Characterisation of the risk:

Not yet established.

The follow-up data available from the Alexion-sponsored clinical trials in complement-mediated TMA, including aHUS patients, are extremely limited to enable any conclusions as of yet.

As of the data lock point of 30 June 2024, no data are yet available in post-authorisation experience.

Severity has not yet been established for ravulizumab.

Risk factors and risk groups:

Patients with known genetic abnormalities in complement genes or known autoantibodies to complement proteins are likely at higher risk (Menne et al 2018).

Preventability:

Increased awareness of the healthcare professionals (HCPs) and patients about the potential risk of TMA complications after discontinuation and their related signs and symptoms are helpful in minimising the impact of the risk.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk profile of ULTOMIRIS is acceptable in light of the anticipated benefits of the therapy and risk minimisation measures in place.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.4 Important potential risk 3: Immunogenicity

Potential mechanisms:

Immunogenicity represents a known effect of various therapeutic biologicals, including monoclonal antibodies. It often presents with the development of ADA. Unwanted immunogenicity results from natural humoral and/or cellular immune response to complex structures of "foreign" molecules. This immune response is influenced by many factors, including immunogenic potential of the molecule and may, or may not be clinically meaningful.

The potential consequences of such immune response range from the transient development of ADA to severe life-threatening conditions, such as cytokine-release syndrome or severe anaphylaxis (Matucci et al 2013), requiring clinical intervention.

Potential clinical consequences also may include decrease in efficacy (eg, development of neutralising ADA) and induction of autoimmunity, including antibodies to the endogenous form of the protein (Casadevall et al 2002, Li et al 2001). The various hypersensitivity reactions (delayed or acute, characterised by several underlying mechanisms) may be one of the clinical consequences of immunogenicity associated with biologicals (Matucci et al 2013).

Evidence source(s) and strength of evidence:

This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including monoclonal antibodies.

Characterisation of the risk:

Across the clinical studies in PNH patients, 1 patient (0.38%) had treatment-emergent ADA. This ADA was transient in nature with low titre and did not correlate with clinical response or adverse events.

Across the clinical studies in aHUS patients, one patient (1.4%) had transient treatment-emergent, low-titre ADA. This ADA was not associated with clinical response or adverse events.

No treatment-emergent ADA-positive findings were observed in gMG patients during the 26-week primary evaluation period.

No patients with NMOSD developed treatment-emergent ADAs during the primary evaluation period. One patient with an ADA-positive sample at baseline had a low titre (1:3) ADA-positive sample at Week 26 of treatment and was considered to have pre-existing immunogenicity.

No positive neutralising antibodies results were observed for any of the ravulizumab treated patients. No impact of immunogenicity on ravulizumab pharmacokinetics or pharmacodynamics was observed.

As of the data lock point of 30 June 2024, 3 cases of immunogenicity with no undesirable clinical outcome were reported from the post-marketing sources. The cumulative post-marketing reporting rate for this risk is approximately 0.01 case per 100 patient-years (3 cases per 27,685.8 patient-years).

As of 30 June 2024, the cumulative post-marketing reporting rate for hypersensitivity is approximately 1.8 cases per 100 patient-years (488 cases per 27,685.8 patient-years). Given the lack of information on ADA in all these cases, it is unknown if these events were related to immunogenicity.

The post-marketing reporting rate of immunogenicity remains stable and lower than that seen in the initial clinical development programme.

The cumulative clinical trial experience since the DIBD for ravulizumab until 30 June 2024 (in all investigated therapeutic areas) provides the cumulative incidence rate for hypersensitivity of approximately 0.2 case per 100 patient-years (6 cases per 3,264.2 patient-years). There were no events of anaphylactic reaction in a clinical trial setting.

In all ADA-positive cases, no clinical signs or symptoms were associated with antibody development, no signs of neutralising effects on pharmacokinetic or pharmacodynamic

parameters were noted, no correlation to clinical response or adverse events was observed and antibody titres were low.

Risk factors and risk groups:

No specific risk factors for the development of immunogenicity have yet been identified.

Preventability:

Immunogenicity reactions are essentially not preventable.

Patients sensitive to ravulizumab, murine proteins or any component of the product cannot initiate treatment with ravulizumab.

In general, certain infusion-related hypersensitivity reactions can be prevented or, at least, minimised by premedication, antipyretics (ibuprofen or paracetamol), and antihistamines (diphenhydramine). No such preventive measures were deemed necessary within the clinical development of ravulizumab.

Impact on the risk-benefit balance of the product:

The risk of immunogenicity is common to all biologicals, introducing a “foreign” entity into the organism. Patients may develop “asymptomatic” ADA which may or may not be clinically meaningful. Development of ADA may cause variable level of loss of drug’s efficacy, but also results in serious adverse drug reactions (various allergic/hypersensitivity reactions in nature). No clinically meaningful outcomes resulting from the development of anti-ravulizumab antibodies were described in the ravulizumab clinical trials. No implications were made also for eculizumab, either in the clinical trial or in the post-marketing setting.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.5 Important potential risk 4: Serious infections

Potential mechanisms:

Ravulizumab mode of action is based on terminal complement (C5) inhibition which is associated with an increased incidence of neisserial infections, as *Neisseria* spp. are primarily cleared by terminal complement components. However, ravulizumab does not inhibit early complement components which are able to clear infections other than caused by *Neisseria* spp.

Evidence source(s) and strength of evidence:

This potential risk is a based on the mode of action of ravulizumab and experience with the use of SOLIRIS (eculizumab). Patients receiving ravulizumab are often at increased risk of infection due to the underlying medical condition or its complications. Therefore, a causative link between serious infections and ravulizumab have not been established. Since causal relationship of serious infections to ravulizumab therapy has not been confirmed in clinical trials, this remains a potential risk.

Characterisation of the risk:

As of the data lock point of 30 June 2024, the cumulative incidence rate for serious infections in clinical trial setting is 13.1 cases per 100 patient-years (428 cases per 3,264.2 patient-years).

As of 30 June 2024, the cumulative post-marketing reporting rate for serious infections is 4.1 cases per 100 patient-years (1,135 cases per 27,685.8 patient-years).

The post-marketing reporting rate remains lower than that seen in the initial clinical development programme.

Serious infections have been reported in patients receiving ravulizumab. Infections may become rapidly serious in immunocompromised patients such as patients with bone marrow disorders, renal failure or receiving immunosuppressive drugs. Patients generally recovered without sequelae after anti-infective treatment. The severity of serious infections ranged from mild to severe. Serious infection does represent a severe condition with a potential for fatal outcome.

Risk factors and risk groups:

Patients with underlying immunodeficiency or acquired conditions (eg, aplastic anaemia or myelodysplastic syndrome in patients with PNH or ESRD in patients with aHUS).

Preventability:

Increased awareness of HCPs and patients about the potential risk of serious infection and the related signs and symptoms of serious infection is helpful in minimising the impact of the risk.

Paediatric patients must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to national vaccination recommendations for each age group.

Ravulizumab should be administered with caution to patients with active systemic infections.

Impact on the risk-benefit balance of the product:

Since this risk seems to be directly associated with the ravulizumab mechanism of action with an increased incidence of *Neisseria* infections, it has a significant impact on the benefit-risk balance of ULTOMIRIS, but acceptable in the light of the anticipated benefits of the therapy.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.6 Important potential risk 5: Malignancies and haematologic abnormalities in PNH patients

Potential mechanisms:

Haematologic malignancy in PNH patients is most likely a manifestation of underlying abnormalities of haematopoietic function. Antitumor immunity is not expected to be affected by ravulizumab.

Evidence source(s) and strength of evidence:

This potential risk is based on the incidence of malignancies in PNH patients treated by SOLIRIS (eculizumab). As the natural evolution of PNH makes PNH patients more prone to development of haematologic abnormalities or malignancies (de Latour et al 2008, Hillmen et al 1995, Socié et al 1996), the role of eculizumab or ravulizumab remains unknown.

Characterisation of the risk:

As of the 30 June 2024, the cumulative incidence rate of malignant cases (both solid and haematologic) in clinical trials is 0.6 cases per 100 patient-years (19 cases per 3,264.2 patient-years) in PNH subjects.

As of the 30 June 2024, the cumulative post-marketing reporting rate of solid malignancies and haematologic abnormalities is approximately 0.5 cases per 100 patient-years (132 cases per 27,685.8 patient-years). Of note, the post-marketing exposure data per indication are not available, and thus, the post-marketing rate was calculated using exposure for all indications and therefore, the above rates are slightly underestimated.

The post-marketing reporting rate remains stable and comparable to the rate seen in the initial clinical development programme.

Malignancies have been reported in patients treated with ravulizumab with seriousness and outcomes not different from what is currently observed in the general population.

Risk factors and risk groups:

Patients with underlying myelodysplastic syndrome or other pre-leukaemic syndromes are at-risk of leukaemia acutisation.

Preventability:

Not preventable.

Impact on the risk-benefit balance of the product:

The potential impact of this risk on the benefit-risk balance of ULTOMIRIS is considered acceptable in light of anticipated benefits of the therapy and overall characteristics of PNH population.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.2 Presentation of missing information

2.7.3.2.1 Missing information: Use in pregnant and breast-feeding women

Evidence source:

There is currently limited experience with the use of ravulizumab during pregnancy or breast-feeding and no known effects of ravulizumab on foetal development during pregnancy or breast-fed child.

The nonclinical studies with a surrogate murine BB5.1 did not show any signs of reproductive or developmental toxicity in the preclinical development programme.

Anticipated risk/consequence of the missing information

Ravulizumab may be used during pregnancy only if benefits of the treatment are expected to outweigh any potential risks. Women of childbearing potential must use effective contraception during treatment and up to 8 months after treatment.

Since many medicinal products (including immunoglobulins) are secreted into human milk, and because of the potential for serious adverse reactions in breast-fed children, breast-feeding should be discontinued during treatment and up to 8 months after treatment.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-6 Summary of safety concerns

Important identified risks	Meningococcal infection
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients
Missing information	Use in pregnant and breast-feeding women

aHUS, atypical haemolytic uraemic syndrome; PNH, paroxysmal nocturnal haemoglobinuria; TMA, thrombotic microangiopathy.

3. PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for meningococcal infection:**

This structured follow-up form is designed to optimise collection of all relevant information associated with the case reports of meningococcal infection to deepen the understanding of the factors leading to this risk associated with ULTOMIRIS.

This form aims to collect detailed information about the patient, concerned medicinal product, patient's history with meningococcal infections and information about past vaccination/antibiotic prophylaxis. It further collects information on laboratory findings (bacteriology, serology, biopsy) and clinical presentation of the event. Finally, information about treatment and outcome of the event are collected.

- **Specific adverse reaction follow-up questionnaires for use in pregnant and breast-feeding women:**

The follow-up on pregnancy, newborns/infants exposed to ULTOMIRIS during pregnancy (up to 3 months after date of birth), and breast-feeding is performed with the use of "Pregnancy Reporting and Outcome Form / Breast Feeding" form. This form is designed to collect general information on the course of pregnancy and breast-feeding, and delivery together with the outcomes for the newborn/infant.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

ALX-PNH-501 (former M07-001) summary

Study short name and title:
ALX-PNH-501 - Characterization of Participants Treated with Ultomiris® and Long-Term Safety Outcomes: an IPIG PNH Registry-based Study

Rationale and study objectives:
Alexion has been the Sponsor of a global PNH Registry (M07-001) since August 2004 and enrolled participants with PNH worldwide, including participants treated with SOLIRIS (eculizumab) since its first approval in 2007. This registry had the ability to actively collect long-term clinical outcomes and safety data related to the treatment of PNH with SOLIRIS or ULTOMIRIS to characterise the long-term safety profile of both therapies.

In 2023, the Alexion PNH Registry began transitioning to the International PNH Interest Group (IPIG) PNH Registry with the objective to move from an industry-sponsored registry to

an academic-led registry database. The IPIG PNH Registry aims to enrol patients with PNH, regardless of the type of PNH-specific therapy they are receiving, to capture data on clinical outcomes, patient reported outcomes, and health resource utilisation on all enrolled patients, as well as long-term safety data of PNH-specific treatments.

Regardless of Alexion's commitment to provide interim safety analysis reporting, enrolled participants will be followed in the IPIG PNH registry for at least 5 years after their enrolment,

The primary objectives of this IPIG-Registry based PASS are:

- To characterise the safety of ULTOMIRIS in participants with PNH.
- To characterise the incidence of targeted clinical outcomes among participants with PNH.

The secondary objectives are:

- To describe the demographic and clinical profile at treatment initiation for ULTOMIRIS treated participants with PNH.
- To assess ULTOMIRIS treatment patterns among participants with PNH.

List of addressed safety concerns:

- Meningococcal infection.
- Serious haemolysis after drug discontinuation in PNH patients.
- Serious infections.
- Malignancies and haematologic abnormalities in PNH patients.
- Use in pregnant and breast-feeding women.

Study design:

Non-interventional cohort study

Study population:

Participants of any age and sex, with PNH with a detected proportion of PNH cells (PNH clone) of at least 1% at registry enrolment, initiating ULTOMIRIS on or after enrolment into the Alexion or IPIG PNH Registries.

Milestones:

- Estimated date for first data extraction is January 2025.
- Estimated date for final study report is July 2025.

Observational aHUS Registry (M11-001) summary

Study short name and title:
M11-001 - Atypical Hemolytic Uremic Syndrome (aHUS) Registry

Rationale and study objectives:
The registry aims to collect and evaluate safety and effectiveness data specific to the use of ravulizumab in aHUS patients and to assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving ravulizumab treatment or other disease management.

List of addressed safety concerns:

- Meningococcal infection.
- Severe TMA complications in aHUS patients after ravulizumab discontinuation.
- Immunogenicity.
- Serious infections.
- Use in pregnant and breast-feeding women.

Study design:
Observational prospective study

Study population:
aHUS patients treated and not treated with ULTOMIRIS.

Milestones:
Every 2 years interim data analysis report.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Characterization of Participants Treated with Ultomiris® and Long-Term Safety Outcomes: an IPIG PNH Registry-based Study ALX-PNH-501 Ongoing	To characterise the safety of ULTOMIRIS in participants with PNH. To characterise the incidence of targeted clinical outcomes among participants with PNH. To describe the demographic and clinical profile at treatment initiation for ULTOMIRIS treated participants with PNH. To assess ULTOMIRIS treatment patterns among participants with PNH.	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Estimated date for first data extraction	January 2025
			Final study report (estimated)	July 2025
Atypical Hemolytic Uremic Syndrome (aHUS) Registry M11-001 Ongoing	To collect and evaluate safety and effectiveness data specific to the use of ravulizumab in aHUS patients. To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving ravulizumab treatment or other disease management.	Meningococcal infection Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Use in pregnant and breast-feeding women	Interim data analysis	Every 2 years interim data analysis report

aHUS, atypical haemolytic uraemic syndrome; EU, European Union; IPIG, International PNH Interest Group; PNH, paroxysmal nocturnal haemoglobinuria; TMA, thrombotic microangiopathy.

4. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

5. PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Meningococcal infection	**Routine risk communication:** SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The need for vaccination (including the need for patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine to receive antibiotic prophylaxis until 2 weeks after vaccination) is recommended in SmPC section 4.4 and PL section 2 Information on educational materials and signs and symptoms of meningococcal infections in included in SmPC section 4.4 Signs and symptoms of meningococcal infection are closely described in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Serious haemolysis after drug discontinuation in PNH patients	**Routine risk communication:** SmPC section 4.4 PL section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Close monitoring of PNH patients who discontinue ravulizumab is recommended and further specified in SmPC section 4.4 and PL section 3. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Severe TMA complications in aHUS patients after ravulizumab discontinuation	**Routine risk communication:** SmPC section 4.4 PL section 3

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Close monitoring of aHUS patient who discontinue ravulizumab is recommended and further specified in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Immunogenicity	**Routine risk communication:** SmPC sections 4.4 and 4.8 **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Serious infections	**Routine risk communication:** SmPC sections 4.3, 4.4 and 4.8 PL sections 2, 3 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A need for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections is included in SmPC section 4.4 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Malignancies and haematologic abnormalities in PNH patients	**Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription
Use in pregnant and breast-feeding women	**Routine risk communication:** SmPC sections 4.6 and 5.3 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for contraception during therapy and up to 8 months after cessation of therapy is specified in SmPC section 4.6 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription

aHUS, atypical haemolytic uraemic syndrome; PL, package leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics; TMA, thrombotic microangiopathy.

5.2 ADDITIONAL RISK MINIMISATION MEASURES

5.2.1 Educational materials

5.2.1.1 Educational materials for healthcare professionals

5.2.1.1.1 Guide for healthcare professionals

Objectives:

To ensure that the HCPs are aware of the risk of meningococcal infections associated with ravulizumab and the need for vaccination against *N meningitidis*.

To instruct the HCPs about careful monitoring and proper management of meningococcal infections.

List of addressed safety concerns:

- Meningococcal infection.

Rationale for the additional risk minimisation activity:

To reinforce to the HCPs the importance of minimising the risk of meningococcal infection and the poor outcomes following the infection.

To instruct the prescribers to monitor all patients for signs and symptoms of meningococcal infection.

To inform the prescribers to educate their patients to seek immediate medical care as soon as they experience any signs and symptoms of meningococcal infections.

Target audience and planned distribution path:

The HCPs guide will be made available to HCPs, in a manner appropriate to how the additional risk minimisation measures will be implemented in each country, where ravulizumab is marketed, and in accordance with the local regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.1.2 Educational material for the patients/parents/caregivers

5.2.1.2.1 Guide for patients/parents/caregivers

Objectives:

To raise awareness in the patients and parents/caregivers of paediatric patients who are prescribed ravulizumab about the detection and proper management of selected safety concerns associated with ULTOMIRIS .

List of addressed safety concerns:

- Meningococcal infection.
- Serious infections
- Severe TMA complication in aHUS-patients after ravulizumab discontinuation

Rationale for the additional risk minimisation activity:

To educate the patients and parents/caregivers of paediatric patients about the main risks associated with ravulizumab treatment especially the risk of meningococcal infection and to seek immediate medical care as soon as they notice any signs and symptoms of meningococcal infections and the need to carry and show the patient card.

It includes a paediatric card that contains safety information for anyone responsible for the care of a child receiving ravulizumab (eg, a teacher, babysitter/nanny, daycare centre staff).

Target audience and planned distribution path:

This guide will be made available to patients/parents/caregivers of paediatric patients in a manner appropriate to each country, where ravulizumab is marketed and in accordance with the local regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.1.2.2 Patient card

Objectives:

To list signs and symptoms of meningococcal infections to the patients/parents/caregivers of the paediatric patients and HCPs to identify potential meningococcal infection and to seek immediately medical care. In addition, when patients present to a physician different than the usual prescriber, it helps to promptly identify potential meningococcal infection and to initiate appropriate antibiotic treatment.

List of addressed safety concerns:

- Meningococcal infection.

Rationale for the additional risk minimisation activity:

Signs and symptoms of meningococcal infections need to be recognised in a timely manner. This card highlights these signs and symptoms as well as the need for seeking immediate medical attention if they occur. The card also emphasises that the patient must receive vaccination or revaccination according to current national vaccination guidelines for vaccination use.

The card also emphasises that the patient must receive vaccination or revaccination according to current national vaccination guidelines for vaccination use.

Target audience and planned distribution path:

- Patients/parents/caregivers
- Physicians other than usual prescribers

The patient card will be made available to patients/parents/caregivers in a manner appropriate to each country, where ravulizumab is marketed, and in accordance with the local regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.2 Annual vaccination reminders for HCPs

Objectives:

To remind the HCPs on an annual basis to verify and ensure that the patient's vaccination against meningococcal infection are still current according to local vaccination guideline.

List of addressed safety concerns:

- Meningococcal infection.

Rationale for the additional risk minimisation activity:

To highlight the importance of an effective vaccination against meningococcal infection to minimise this important risk. Vaccination against available meningococcal serotypes prior initiation of ravulizumab therapy represents one of the essential risk minimisation activity.

Target audience and planned distribution path:

Vaccination reminder for prescribers or pharmacists who prescribe/dispense ravulizumab, will be sent in a manner appropriate to each country where ravulizumab is marketed and in accordance with the local regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The MAH ensures the reminder is sent annually to the HCPs.

Removal of additional risk minimisation activity – controlled distribution

Rationale for the removal:

The additional risk minimisation measures have been revised as described in Section 5.2 and the controlled distribution measure, previously in place since the initial marketing authorisation in the EU has been removed.

Based on the cumulative analysis of cases of meningococcal infection, the evaluation of the current additional risk minimisation measures (process indicators such as knowledge and understanding of the risk by the HCPs and outcome indicators such as rates of meningococcal infection over time), the evidence that vaccination guidance for complement inhibitors has become a standard healthcare practice and the evaluation of the unintended outcomes, the initially implemented additional risk minimisation measures, which included controlled distribution as one of the measures, have been revised.

The revised additional risk minimisation measures will continue to use the educational materials focusing on addressing the risk of meningococcal infection and removal of other safety concerns given that some of these risks are well known by the HCPs.

The educational tools for HCPs will continue to include a guide for HCPs. The educational tools for patients will continue to include a guide for patients/parents/caregivers and a patient card. The annual vaccination reminders will be continued to be sent to HCPs.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Meningococcal infection	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 The need for vaccination (including the need for patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine to receive antibiotic prophylaxis until 2 weeks after vaccination) is recommended in in SmPC section 4.4 and PL section 2 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription **Additional risk minimisation measures:** Educational materials Guide for healthcare professionals Guide for patients/parents/caregivers Patient card Annual vaccination reminder	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** ALX-PNH-501 (final report: July 2025) aHUS registry (M11-001)

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious haemolysis after drug discontinuation in PNH patients	**Routine risk minimisation measures:** SmPC section 4.4 PL section 3 Monitoring of patients who discontinued ULTOMIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** ALX-PNH-501 (final report: July 2025)
Severe TMA complications in aHUS patients after ravulizumab discontinuation	**Routine risk minimisation measures:** SmPC section 4.4 Restricted medical prescription **Additional risk minimisation measures:** Guide for patients/parents/caregivers	**Additional pharmacovigilance activities:** aHUS registry (M11-001)
Immunogenicity	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 Restricted medical prescription **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** aHUS registry (M11-001)
Serious infections	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8 PL sections 2, 3 and 4 Recommendations for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2. Restricted medical prescription **Additional risk minimisation measures:**	**Additional pharmacovigilance activities:** ALX-PNH-501 (final report: July 2025) aHUS registry (M11-001)

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Guide for patients/parents/caregivers	
Malignancies and haematologic abnormalities in PNH patients	**Routine risk minimisation measures:** Restricted medical prescription **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** ALX-PNH-501 (final report: July 2025)
Use in pregnant and breast-feeding women	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3 PL section 2 Recommendations on contraception in SmPC section 4.8 and PL section 2 Restricted medical prescription **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** ALX-PNH-501 (final report: July 2025) aHUS registry (M11-001)

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis, NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria; PL, package leaflet; SmPC, summary of product characteristics.

6. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR RAVULIZUMAB

Summary of risk management plan for ULTOMIRIS (ravulizumab)

This is a summary of the risk management plan (RMP) for ULTOMIRIS. The RMP details important risks of ULTOMIRIS, how these risks can be minimised, and how more information will be obtained about ULTOMIRIS's risks and uncertainties (missing information).

ULTOMIRIS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ULTOMIRIS should be used.

Important new concerns or changes to the current ones will be included in updates of ULTOMIRIS's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

ULTOMIRIS is authorised for paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uraemic syndrome (aHUS), generalised myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD) (see SmPC for the full indication). It contains ravulizumab as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of benefits can be found in EPAR of ULTOMIRIS, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of ULTOMIRIS, together with measures to minimise such risks and the proposed studies for learning more about ULTOMIRIS' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In the case of ULTOMIRIS, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ULTOMIRIS is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of ULTOMIRIS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ULTOMIRIS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

Important identified risks	Meningococcal infection
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients
Missing Information	Use in pregnant and breast-feeding women

aHUS, atypical haemolytic uraemic syndrome; PNH, paroxysmal nocturnal haemoglobinuria; TMA, thrombotic microangiopathy.

6.2.2 Summary of important risks

Table 6-2 Meningococcal infection

Evidence for linking the risk to the medicine	This important identified risk is based on the ravulizumab mode of action, findings from the clinical trial development programme for ravulizumab, post-marketing experience with ravulizumab and on the long term experience with eculizumab (Soliris). The link between terminal complement components deficiency states and (serious) infections caused by *N meningitidis* is firmly established and evidenced by the scientific literature.
Risk factors and risk groups	Main risk factors for these infections include: • Genetic deficiency or therapeutic inhibition of terminal complement • Lack of commercially available vaccine against certain meningococcus serogroup • (Partial) resistance of meningococcal strain to prophylactic antibiotics • Professionals who are exposed to environments of greater risk for meningococcal disease • Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis* • Military personnel during recruit training (military personnel may be at increased risk of meningococcal infections when accommodated in close quarters) • Daycare centre workers • Living on a college or university campus • Travelling to endemic areas for meningococcal meningitis (eg, India, Sub Saharan Africa, pilgrimage to Saudi Arabia for Hajj)
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 The need for vaccination (including the need for patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine to receive antibiotic prophylaxis until 2 weeks after vaccination) is recommended in in SmPC section 4.4 and PL section 2 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription **Additional risk minimisation measures:** Educational materials Guide for healthcare professionals

Table 6-2 Meningococcal infection

	Guide for patients/parents/caregivers Patient card Annual vaccination reminder
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ALX-PNH-501 aHUS registry (M11-001) See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

aHUS, atypical haemolytic uraemic syndrome; PL, package leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics.

Table 6-3 Serious haemolysis after drug discontinuation in PNH patients

Evidence for linking the risk to the medicine	This is a theoretical possibility based on the ravulizumab mode of action, nature of PNH, and experience with the use (and discontinuation) of Soliris (eculizumab).
Risk factors and risk groups	No risk factors have yet been identified.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 PL section 3 Monitoring of patients who discontinued ULTOMIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ALX-PNH-501 See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

PL, package leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics.

Table 6-4 Severe TMA complications in aHUS patients after ravulizumab discontinuation

Evidence for linking the risk to the medicine	This potential risk is based on the long term observational prospective study with eculizumab (Study C11-003). Discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study with eculizumab indicate that patients who discontinued eculizumab experienced a higher rate of TMA recurrence (13.5-fold) and showed a

Table 6-4 Severe TMA complications in aHUS patients after ravulizumab discontinuation

	trend toward reduced renal function compared to patients who continued eculizumab treatment. No such effects have been observed in the clinical development programme for ravulizumab in aHUS patients. Therefore, this represents a potential risk for ULTOMIRIS.
Risk factors and risk groups	Patients with known genetic abnormalities in complement genes or known autoantibodies to complement proteins are likely at higher risk.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 Restricted medical prescription **Additional risk minimisation measures:** Guide for patients/parents/caregivers
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** aHUS registry (M11-001) See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

aHUS, atypical haemolytic uraemic syndrome; SmPC, summary of product characteristics; TMA, thrombotic microangiopathy.

Table 6-5 Immunogenicity

Evidence for linking the risk to the medicine	This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including monoclonal antibodies.
Risk factors and risk groups	No specific risk factors for the development of immunogenicity have yet been identified.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** aHUS registry (M11-001) See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

aHUS, atypical haemolytic uraemic syndrome; SmPC, summary of product characteristics.

Table 6-6 Serious infections

Evidence for linking the risk to the medicine	This risk is a based on the ravulizumab mode of action and experience with the use of Soliris (eculizumab). Since relevance of serious infections to ravulizumab therapy has not been confirmed in clinical trials, this remains a potential risk.
Risk factors and risk groups	Patients with underlying immunodeficiency or acquired conditions (eg, aplastic anaemia or myelodysplastic syndrome in patients with PNH or end-stage renal disease in patients with aHUS) or due to exposure to immunosuppressive drugs (eg, long-term use of corticosteroids and/or immunosuppressive agents in patients with gMG and NMOSD).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8 PL sections 2, 3 and 4 Recommendations for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2. Restricted medical prescription **Additional risk minimisation measures:** Guide for patients/parents/caregivers
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ALX-PNH-501 aHUS registry (M11-001) See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PL, package leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics.

Table 6-7 Malignancies and haematologic abnormalities in PNH patients

Evidence for linking the risk to the medicine	This potential risk is based on the incidence of malignancies in PNH patients treated by Soliris (eculizumab). As the natural evolution of PNH makes PNH patients more prone to development of haematologic abnormalities or malignancies, the role of eculizumab or ravulizumab remains unknown.
Risk factors and risk groups	Patients with underlying myelodysplastic syndrome or other pre-leukaemic syndromes are at-risk of leukaemia acutisation.
Risk minimisation measures	**Routine risk minimisation measures:** Restricted medical prescription **Additional risk minimisation measures:** None

Table 6-7 Malignancies and haematologic abnormalities in PNH patients

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ALX-PNH-501 See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

PNH, paroxysmal nocturnal haemoglobinuria.

Table 6-8 Use in pregnant and breast-feeding women

Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3 PL section 2 Recommendations on contraception in SmPC section 4.8 and PL section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ALX-PNH-501 aHUS registry (M11-001) See section 6.2.3 of this summary for an overview of the post-authorisation development plan.

aHUS, atypical haemolytic uraemic syndrome; PL, package leaflet; SmPC, summary of product characteristics.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ULTOMIRIS.

6.2.3.2 Other studies in post-authorisation development plan

ALX-PNH-501

Purpose of the study: The International PNH Interest Group (IPIG)-registry based post-authorisation safety study aims to characterise the safety of ULTOMIRIS and the incidence of targeted clinical outcomes among participants with PNH.

List of addressed safety concerns:

- Meningococcal infection
- Serious haemolysis after drug discontinuation in PNH patients
- Serious infections
- Malignancies and haematologic abnormalities in PNH patients
- Use in pregnant and breast-feeding women.

aHUS registry (M11-001)

Purpose of the study: The registry aims to collect and evaluate safety and effectiveness data specific to the use of ravulizumab in aHUS patients and to assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving ravulizumab treatment or other disease management.

List of addressed safety concerns:

- Meningococcal infection
- Severe TMA complications in aHUS patients after ravulizumab discontinuation
- Immunogenicity
- Serious infections
- Use in pregnant and breast-feeding women.

7. PART VII: ANNEXES

ANNEX 4: Specific adverse drug reaction follow-up forms

- *Global Pharmacovigilance Suspected/Confirmed Meningococcal Case Questionnaire*
- *Pregnancy Reporting and Outcome Form / Breast Feeding*

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Alexion Manufacturer Number:	

Date of Birth: *(DD/MMM/YYYY)*

Age (if known):

Or Age Category:

☐ Child (<12 years) ☐ Adolescent (12-17 years) ☐ Adults (18-65 years) ☐ Elderly (>65 years)

Gender:

☐ Female ☐ Male ☐ Prefer not to disclose

☐ Intersex ☐ Transgender

Weight: ☐ lbs. ☐ kgs.

Height: ☐ cm. ☐ in.

Ethnicity: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Not Hispanic or Latino ☐ Hispanic or Latino

☐ Not Reported ☐ Unknown

Race: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Aboriginal or Torres Strait Islander ☐ Caucasian

☐ African American ☐ Native Hawaiian or Pacific Islander

☐ American Indian or Alaska Native ☐ Not Reported

☐ Asian ☐ Unknown

☐ Black

☐ Other *(Specify)*

Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:**

(DD/MMM/YYYY)

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

☐ Other *(Specify)*

Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:**

(DD/MMM/YYYY)

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

☐ Other *(Specify)*

Patient History

Previous history of meningococcal infection? ☐ Yes ☐ No ☐ Unknown

(please describe)

Risk factor for meningococcal infection? ☐ Yes ☐ No ☐ Unknown

(please describe)

(e.g., Medical condition, exposure to laboratory, industry, close quarters, college campus, daycare workers, military, living in proximity or recent travel to endemic areas)

Meningococcal Vaccination ☐ Yes *(provide vaccine name and date below)* ☐ No ☐ Unknown

Was the patient vaccinated per Advisory Committee on Immunization Practices (ACIP) guidelines?
(Applicable for US only)

☐ Yes ☐ No ☐ Unknown

Was the patient vaccinated according to current national vaccination guidelines?
(Applicable for ex-US only)

☐ Yes ☐ No ☐ Unknown ☐ Not Applicable

Vaccine Name: ☐ Initial Vaccination date:

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

		☐Booster	Vaccination date:	*(DD/MMM/YYYY)*
Vaccine Name:		☐Initial	Vaccination date:	*(DD/MMM/YYYY)*
		☐Booster	Vaccination date:	*(DD/MMM/YYYY)*
Vaccine Name:		☐Initial	Vaccination date:	*(DD/MMM/YYYY)*
		☐Booster	Vaccination date:	*(DD/MMM/YYYY)*
Vaccine Name:		☐Initial	Vaccination date:	*(DD/MMM/YYYY)*
		☐Booster	Vaccination date:	*(DD/MMM/YYYY)*

Antibiotic prophylaxis: ☐Yes ☐No

(If yes) Antibiotic Name / Active substance: Dosage / frequency:

Start date: *(DD/MMM/YYYY)* Stop date: *(DD/MMM/YYYY)* ☐ Ongoing

Is the patient compliant with their antibiotic prophylaxis? ☐ Yes ☐ No ☐ Unknown

Bacteriological work up

CSF: *Direct Exam Results:*

CSF: *Culture Results:*

CSF: *PCR Results:*

Blood: *Direct Exam Results:*

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Blood: *Culture Results:*

Blood: *PCR Results:*

Clinical Presentation

Description of initial clinical signs and/or symptoms patient has presented with:

Onset Date of first symptom(s) *(DD/MMM/YYYY)*

Malaise	☐ Yes ☐ No	
Myalgia	☐ Yes ☐ No	
Fever	☐ Yes ☐ No	*(If yes, please provide temp)*
Hypothermia	☐ Yes ☐ No	*(If yes, please provide temp)*
Headache	☐ Yes ☐ No	
Neck stiffness	☐ Yes ☐ No	
Photophobia	☐ Yes ☐ No	
Vomiting	☐ Yes ☐ No	
Confusion	☐ Yes ☐ No	
Chills	☐ Yes ☐ No	
Convulsions	☐ Yes ☐ No	
Rash	☐ Yes ☐ No	*(If yes, please specify type and localization)*
Other	☐ Yes ☐ No	*(Please specify)*

Patients who receive(d) Antibiotic Prophylaxis Only:
Minimum Inhibitory Concentration (MIC):

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347
or clinicalsae@alexion.com (for clinical trials only)

Serology

Neisseria meningitidis serogroup / serotype:

☐ A ☐ B ☐ C ☐ W135 ☐ X ☐ Y ☐ Z

Other:

(specify)

Neisseria meningitidis serosubtype:
(if available)

Neisseria meningitidis Genotyping (MLST):
(if available)

Meningococcal Antigen Typing System (MATS) assay (For serogroup B infection in patients vaccinated by 4CMenB):

Skin biopsy culture:

☐ Done
☐ Not done

If done, results:

Treatment of the event

Antibiotic Name:

Start date: *(DD/MMM/YYYY)*

Stop date: *(DD/MMM/YYYY)*

☐ Ongoing

Other medication:

Medication Name:

Start date:

Stop date:

☐ Ongoing

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

(DD/MMM/YYYY) *(DD/MMM/YYYY)*

Other supportive treatment:

Was the patient admitted to the ICU? ☐ Yes ☐ No ☐ Unknown

Did the patient experience or require any of the following (select all that apply):

☐ Any organ system failure *(specify)*

☐ Mechanical ventilation

☐ Medication (vasopressors) to support blood pressure *(specify)*

Outcome

☐ Unknown

☐ Recovered ☐ Recovered with sequelae *(specify sequelae)* Date Recovered: (DD/MMM/YYYY)

☐ Ongoing ☐ Fatal *(Specify cause of death)* Date of Death: (DD/MMM/YYYY)

Additional Comments:

Name of Individual Completing the Form Designation

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347
or clinicalsae@alexion.com (for clinical trials only)

Contact Information
Date Form Completed

Revision History

Version Number	Change Type (New, Revised or Admin)	Revision Summary	Justification
1.0	New	Initial Release	N/A
2.0	Revised	Form Updated	Additional fields added
3.0	Revised	Form Updated	Due to Danicopan approval, form updated to include multiple product entries

Pregnancy / Breastfeeding Reporting and Outcome Form

1. Please complete and send Section I (p1-3) at start of pregnancy depending on report type to either…

☐ *Post-Marketing Email: AdverseEventReporting@alexion.com*

OR

☐ *Clinical Trials/Studies Email: ClinicalSAE@alexion.com*

2. Please continue to report both immediately post-delivery and at three months post-delivery

3. Please add additional notes, if necessary, into section IV at the bottom of page 4.

I Pre-delivery

A) General Information				
A0	Suspect Drug: Action taken with suspect drug in response to pregnancy:	Indication: Dosage of drug prior to discovery of pregnancy:	Adjusted dosage of drug since discovery of pregnancy:	Date of last drug administration before pregnancy was noticed. ____/____/____ dd /mmm /
A1	Patient ID *(if applicable):*	Pregnant: Patient ☐ Patient's partner ☐	Date pregnancy was noticed	Estimated date of delivery ____/____/____ dd / mmm /
A2	Mother's date of birth or Age	____/____/____ or ____ dd / mmm / yyyy	Height: ☐ cm ☐ ft/inches	Weight: ____ ☐ kg ☐ lbs
A3	Source of information for this report (Reporter)	☐ = (Pregnant) woman ☐ = Primary care physician/Investigator ☐ = Obstetrician ☐ = Pediatrician ☐ = Other:		
A4	Date of this Report (current date)	____/____/____ dd / mmm / yyyy		
A5	Name, Address and email of Reporter			
A6	Name, Address and email of Gynecologist-obstetrician (if applicable)			

Pregnancy / Breastfeeding Reporting and Outcome Form

A7	Name and address of place of planned delivery	

B) Maternal Information		
Obstetrical History		
B1	Previous pregnancies	N = _____
B2	Outcome of previous pregnancies (insert digits if multiple pregnancies)	☐ = Live birth ☐ = Miscarriage ☐ = Elective termination ☐ = Late fetal death ☐ = Ectopic pregnancy ☐ = Molar
B3	Previous pregnancy complications:	☐ = None ☐ = _____
B4	Previous fetal / neonatal abnormalities and	☐ = Yes _____ ☐ = None
B5	Medical History	☐ = None ☐ = Hypertension ☐ = Diabetes ☐ = Seizures ☐ = Thyroid disorder ☐ = Asthma ☐ = Allergic disease ☐ = Heart Disease ☐ = Depression ☐ = Other psychiatric disorder ☐ = Sexual transmitted disease ☐ = Hepatitis ☐ = HIV / AIDS
B6	Family history	☐ = None ☐ = History of congenital abnormality ☐ = Psychomotor retardation in family
B7	Consanguinity between parents	☐ = None ☐ Degree of relationship:
Current Pregnancy		
B8	Date of Last Menstrual Period (LMP*)	____/_____/_____ dd /mmm / yyyy
B9	Gestational age at the time of last study drug intake	_____weeks _____ days based on ☐ = Ultrasound ☐ = LMP*
B10	Number of fetuses	N = _____
B11	Contraceptive method(s) used before pregnancy	☐ = None ☐ = Oral contraceptive ☐ = Other _____
B12	Recreational drug use	☐ = Tobacco ☐ = Alcohol ☐ = Illicit drug (specify amount and when stopped)
B13	Positive serology tests	☐ = None ☐ = Rubella ☐ = Toxoplasmosis ☐ = Other
Please fill out B14-B17 for initial and follow-up information:		

B14	Concomitant medication (including over-the-counter medication, supplements, vitamins)	Initi al: Foll
B15	Complications during pregnancy and date (including any adverse drug reactions) Please report further complications on page 4	Initial ☐ = None ☐ = (If any: document on last page) Follow-up ☐ = None ☐ = (If any: document on last page)
B16	Disease course(s) during pregnancy and any complications Please indicate for all complications listed in B17.	Initial ☐ = None ☐ = (If any: document on last page) Follow-up: ☐ = None ☐ = (If any: document on
B17	Antenatal check-up (specify dates and results), e.g. fetal ultrasound, serum markers (AFP etc), chorionic biopsy, amniocentesis	Initial: ☐ = No path. findings ☐ = (document on last page) Follow-up: ☐ = No path. findings ☐ = (document on last page)
	_____/_____/_____ dd / mmm / yyyy _____ Reporter's Signature Date (Initial)	_____/_____/_____ dd /mmm / yyyy _____ Reporter's Signature Date (Follow Up)

II Post-delivery

C) **Delivery and Neonatal Information** (Initial) - Please also complete B14-B17 if applicable			
C1	Source and date of information		____/_____/_____ dd/ mmm / yyyy
C2	Mode of delivery	☐ = Spontaneous ☐ = Caesarian section ☐ = Other	
C3	Labor / Delivery complications	☐ = None ☐ Fetal distress ☐ Amniotic fluid abnormal ☐ Abnormal placenta ☐ = Other	
C4	Outcome of pregnancy	☐ = Live birth ☐ = Miscarriage ☐ = Elective termination ☐ = Late fetal death ☐ = Ectopic pregnancy ☐ = Molar pregnancy	
C5	Date of delivery	___/_____/_____ dd /mmm / yyyy	Gender: ☐ = Male ☐ = Female
C6	Gestational age at birth	_____ weeks	
C7	Weight at birth	_____ ☐ kg ☐ lbs	

Pregnancy / Breastfeeding Reporting and Outcome Form

C) **Delivery and Neonatal Information** (Initial) - Please also complete B14-B17 if applicable		
C8	Length	_____ ☐ cm ☐ inches
C9	Head circumference	_____ ☐ cm ☐ inches
C10	Malformation/anomalies diagnosed at birth	☐ = None ☐ = Other:
C11	APGAR Score	APGAR Score 1 APGAR Score 2
C12	Admission to intensive care unit?	☐ = No ☐ = Yes:
C13	Neonatal illness, hospitalization, drug therapies	☐ = None ☐ = Other:
C14	Breastfeeding	☐ = No ☐ = Yes: Start date _____/_____/_____ Stop date _____/_____/_____ dd /mmm / yyyy dd /mmm / yyyy Did the breastfed infant experience any adverse events or side effects ☐ = No

D) Fetal Information in case of elective termination, spontaneous abortion, and late fetal death			
D1	Source and date of information		_____/_____/_____ dd/mmm/yyyy
D2	Reason for termination (If applicable)		
D3	Gestational age at termination	_____weeks	
D4	Results of physical examination (gender, external anomalies) and pathology	_____	

III Follow-up - Three months after birth

1	Source and date of information		_____/_____/_____ dd/mmm/yyyy
2	Malformation/anomalies diagnosed since initial report	☐ = None ☐ = Other:	
3	Infant illnesses hospitalizations, drug therapies	☐ = None ☐ = Other:	
_____ Reporter's Signature		_____/_____/_____ dd/ mmm /yyyy	

IV Additional Notes

Document History

Version Number	Change Type *(New, Revised or Admin)*	Revision Summary	Justification
2.0	Revised	ALXN-SOP-0003874 removed from title and replaced with ALXN-SOP-0003872	ALXN-SOP-0003874 Obsolescence
3.0	Admin	To correct the viewable rendition	Deviation PR#156705

ANNEX 6: Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

Educational materials for healthcare professionals

- The Summary of Product Characteristics
- Guide for healthcare professionals

Guide for healthcare professionals

- Treatment with ravulizumab increases the risk of meningococcal infections.
- The need for patients to be vaccinated against N. meningitidis two weeks prior to receiving ravulizumab and/or to receive antibiotic prophylaxis.
- Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- The need for the prescriber to educate patients/parents/caregivers about the risk of meningococcal infections associated with ravulizumab treatment, awareness of signs and symptoms and what actions to take.
- The need for the prescriber to monitor all patients for signs and symptoms of meningococcal infections.
- The need for the prescriber to instruct patients to carry the patient card and to tell any healthcare professional that they are receiving treatment with ravulizumab.

Educational materials for patients/parents/caregivers

- Patient Product Information
- Guide for patient/parent/caregiver
- Patient card

Guide for patient/parent/caregiver

- Treatment with ravulizumab increases the risk of meningococcal infections.
- The importance of meningococcal vaccination prior to treatment with ravulizumab and/or to receive antibiotic prophylaxis.
- The patient must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- Awareness about the signs and symptoms of meningococcal infections and the need to obtain urgent medical care.

- The importance of patient card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with ravulizumab.
- Risk of severe TMA complications following discontinuation/postponement of ravulizumab administration, their signs and symptoms and the recommendation consult the prescriber before discontinuing/postponing ravulizumab administration (aHUS only)
- Potential risks of severe, non-neisserial infections in patients treated with ravulizumab.

Patient card

- Statement that the patient is receiving ravulizumab and the risk of meningococcal infections.
- Signs and symptoms of a meningococcal infection.
- Warning message to seek immediate medical care if above are present.
- Statement that the patient must receive vaccination and revaccination according to current national guidelines for vaccination use. The vaccination and re-vaccination dates should be included on the patient card.
- Contact details where a healthcare professional can receive further information.

Annual vaccination reminders for HCPs

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

LIST OF REFERENCES

Al-Ani F, Chin-Yee I, Lazo-Langner A. Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations. Ther Clin Risk Manag. 2016; 12:1161-1170.

Anil R, Kumar A, Alaparthi S, Sharma A, Nye JL, Roy B et al. Exploring outcomes and characteristics of myasthenia gravis: Rationale, aims and design of registry - The EXPLORE-MG registry. J Neurol Sci. 2020; 414:116830.

Ardissino G, Salardi S, Colombo E, Testa S, Borsa-Ghiringhelli N, Paglialonga F et al. Epidemiology of haemolytic uremic syndrome in children. Data from the North Italian HUS network. Eur J Pediatr. 2016; 175(4):465-473.

Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. Neurology. 2011; 76(18):1589-1595.

Bichuetti DB, Lemos MD, Castro I, Carvalho GB, Carvalho RS, Abdala N et al. Neuromyelitis optica shorter lesion can cause important pyramidal deficits. J Neurol Sci. 2015; 355(1-2):189-192.

Bichuetti DB, Lobato de Oliveira EM, Oliveira DM, Amorin de Souza N, Gabbai AA. Neuromyelitis optica treatment: analysis of 36 patients. Arch Neurol. 2010; 67(9):1131-1136.

Borisow N, Kleiter I, Gahlen A, Fischer K, Wernecke K-D, Pache F et al. Influence of female sex and fertile age on neuromyelitis optica spectrum disorders. Mult Scler J. 2016; 23(8):1092-1103.

Boscoe AN, Xin H, L'Italien GJ, Harris LA, Cutter GR. Impact of Refractory Myasthenia Gravis on Health-Related Quality of Life. J Clin Neuromuscul Dis. 2019; 20(4):173-181.

Bukhari W, Prain KM, Waters P, Woodhall M, O'Gorman CM, Clarke L et al. Incidence and prevalence of NMOSD in Australia and New Zealand. J Neurol Neurosurg Psychiatry. 2017; 88(8):632-638.

Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006; 108(4):1267-1279.

Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol. 2010; 10:46.

Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002; 346(7):469-475.

Constantinescu AR, Bitzan M, Weiss LS, Christen E, Kaplan BS, Cnaan A et al. Non-enteropathic hemolytic uremic syndrome: causes and short-term course. Am J Kidney Dis. 2004; 43(6):976-982.

Cossburn M, Tackley G, Baker K, Ingram G, Burtonwood M, Malik G et al. The prevalence of neuromyelitis optica in South East Wales. Eur J Neurol. 2012; 19(4):655-659.

Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, Mandrekar J et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology. 2011; 77(7):659-666.

de Latour RP, Mary JY, Salanoubat C, Terriou L, Etienne G, Mohty M et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. Blood. 2008; 112(8):3099-3106.

Devos T, Meers S, Boeckx N, Gothot A, Deeren D, Chatelain B et al. Diagnosis and management of PNH: Review and recommendations from a Belgian expert panel. Eur J Haematol. 2018; 101(6):737-749.

Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B et al. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol. 2010; 21(12):2180-2187.

Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: A single-arm, open-label trial. Am J Kidney Dis. 2016.

Fakhouri F, Roumenina L, Provot F, Sallee M, Caillard S, Couzi L et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol. 2010; 21(5):859-867.

Fang F, Sveinsson O, Thormar G, Granqvist M, Askling J, Lundberg IE et al. The autoimmune spectrum of myasthenia gravis: a Swedish population-based study. J Intern Med. 2015; 277(5):594-604.

Figueroa JE and Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev. 1991; 4(3):359-395.

Flanagan EP, Cabre P, Weinshenker BG, St Sauver J, Jacobson DJ, Majed M et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Ann Neurol. 2016.

Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaime F, Dragon-Durey MA, Ngo S et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol. 2013; 8(4):554-562.

Füreder W, Sperr WR, Heibl S, Zebisch A, Pfeilstöcker M, Stefanzl G et al. Prognostic factors and follow-up parameters in patients with paroxysmal nocturnal hemoglobinuria (PNH): experience of the Austrian PNH network. Ann Hematol. 2020; 99(10):2303-2313.

Gattellari M, Goumas C, Worthington JM. A national epidemiological study of Myasthenia Gravis in Australia. Eur J Neurol. 2012; 19(11):1413-1420.

Geerdink LM, Westra D, van Wijk JA, Dorresteijn EM, Lilien MR, Davin JC et al. Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics. Pediatr Nephrol. 2012; 27(8):1283-1291.

Gilhus NE and Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015; 14(10):1023-1036.

Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2008; 37(2):141-149.

Hamid SHM, Whittam D, Mutch K, Linaker S, Solomon T, Das K et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. J Neurol. 2017; 264(10):2088-2094.

Hansen DL, Moller S, Andersen K, Gaist D, Frederiksen H. Increasing incidence and prevalence of acquired hemolytic anemias in Denmark, 1980-2016. Clin Epidemiol. 2020; 12:497-508.

Harris L, Aban IB, Xin H, Cutter G. Employment in refractory myasthenia gravis: A Myasthenia Gravis Foundation of America Registry analysis. Muscle Nerve. 2019; 60(6):700-706.

Hehir MK and Silvestri NJ. Generalized Myasthenia Gravis: Classification, Clinical Presentation, Natural History, and Epidemiology. Neurol Clin. 2018; 36(2):253-260.

Heitlinger E. Learnings from over 25 years of PNH experience: the era of targeted complement inhibition. Blood Rev. 2013; 27 Suppl 1:S1-6.

Hendricks TM, Bhatti MT, Hodge DO, Chen JJ. Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study. Am J Ophthalmol. 2019; 205:99-105.

Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017; 3:17028.

Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013; 121(25):4985-4996.

Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995; 333(19):1253-1258.

Holroyd KB, Manzano GS, Levy M. Update on neuromyelitis optica spectrum disorder. Curr Opin Ophthalmol. 2020; 31(6):462-468.

Huda R, Tuzun E, Christadoss P. Targeting complement system to treat myasthenia gravis. Rev Neurosci. 2014; 25(4):575-583.

Jalbert JJ, Chaudhari U, Zhang H, Weyne J, Shammo JM. Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the US. Blood. 2019; 134(Supplement 1):3407-3407.

Jang JH, Kim JS, Yoon SS, Lee JH, Kim YK, Jo DY et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): Results from a Korean PNH registry. J Korean Med Sci. 2016; 31(2):214-221.

Jarius S, Ruprecht K, Wildemann B, Kuempfel T, Ringelstein M, Geis C et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. J Neuroinflammation. 2012; 9(1):14.

Jenssen GR, Hovland E, Bjerre A, Bangstad HJ, Nygard K, Vold L. Incidence and etiology of hemolytic-uremic syndrome in children in Norway, 1999-2008--a retrospective study of hospital records to assess the sensitivity of surveillance. BMC Infect Dis. 2014; 14:265.

Joensen P. Myasthenia gravis incidence in a general North Atlantic isolated population. Acta Neurol Scand. 2014; 130(4):222-228.

Kavanagh D, Goodship TH, Richards A. Atypical haemolytic uraemic syndrome. Br Med Bull. 2006; 77-78:5-22.

Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood. 2011; 117(25):6786-6792.

Kim W, Kim SH, Kim HJ. New insights into neuromyelitis optica. J Clin Neurol. 2011; 7(3):115-127.

Kimbrough DJ, Fujihara K, Jacob A, Lana-Peixoto MA, Leite MI, Levy M et al. Treatment of neuromyelitis optica: Review and recommendations. Mult Scler Relat Disord. 2012; 1(4):180-187.

Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. JAMA Neurol. 2014; 71(3):276-283.

Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Wegner B et al. Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. Ann Neurol. 2016; 79(2):206-216.

Kremer L, Mealy M, Jacob A, Nakashima I, Cabre P, Bigi S et al. Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients. Mult Scler. 2014; 20(7):843-847.

Kuo CF, Grainge MJ, Valdes AM, See LC, Luo SF, Yu KH et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern Med. 2015; 175(9):1518-1526.

Lee JW, Jang JH, Kim JS, Yoon SS, Lee JH, Kim YK et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. Int J Hematol. 2013; 97(6):749-757.

Lefter S, Hardiman O, Ryan AM. A population-based epidemiologic study of adult neuromuscular disease in the Republic of Ireland. Neurology. 2017; 88(3):304-313.

Lemaire M, Fremeaux-Bacchi V, Schaefer F, Choi M, Tang WH, Le Quintrec M et al. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet. 2013; 45(5):531-536.

Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001; 98(12):3241-3248.

Licht C, Ardissino G, Ariceta G, Cohen D, Cole JA, Gasteyger C et al. The global aHUS registry: methodology and initial patient characteristics. BMC Nephrol. 2015; 16:207-207.

Ling CS, Shen ML, Wang Y, Cai WK, Lin XQ, Huang Q et al. The associations of HLA-DRB1 gene polymorphisms with late-onset myasthenia gravis: a meta-analysis. Neurol Sci. 2020; 41(5):1041-1049.

Loirat C and Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6:60.

M11-001. An observational, noninterventional multicenter, multinational study of patients with atypical hemolytic-uremic syndrome. Alexion Pharmaceuticals, Inc.; 2015.

MacNeil JR, Blain AE, Wang X, Cohn AC. Current epidemiology and trends in meningococcal disease-United States, 1996-2015. Clin Infect Dis. 2018; 66(8):1276-1281.

Maga TK, Nishimura CJ, Weaver AE, Frees KL, Smith RJ. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. Hum Mutat. 2010; 31(6):E1445-1460.

Mantegazza R, Vanoli F, Frangiamore R, Cavalcante P. Complement Inhibition for the Treatment of Myasthenia Gravis. Immunotargets Ther. 2020; 9:317-331.

Marx A, Pfister F, Schalke B, Saruhan-Direskeneli G, Melms A, Ströbel P. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev. 2013; 12(9):875-884.

Matucci A, Petroni G, Nencini F, Pratesi S, Maggi E, Vultaggio A. Anti-drug antibodies and clinical implications. Clin Dermatol. 2013; 2(2):77-80.

McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. Neuroepidemiology. 2010; 34(3):171-183.

Mealy MA, Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. JAMA Neurol. 2014; 71(3):324-330.

Menne J, Delmas Y, Fakhouri F, Kincaid JF, Licht C, Minetti EE et al. Eculizumab prevents thrombotic microangiopathy in patients with atypical haemolytic uraemic syndrome in a long-term observational study. Clin Kidney J. 2018; 12(2):196-205.

Menne J, Delmas Y, Fakhouri F, Licht C, Lommele A, Minetti EE et al. Outcomes in patients with atypical hemolytic uremic syndrome treated with eculizumab in a long-term observational study. BMC Nephrol. 2019; 20(1):125.

Menon D, Barnett C, Bril V. Novel Treatments in Myasthenia Gravis. Front Neurol. 2020; 11:538.

Meriggioli MN and Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009; 8(5):475-490.

Micheletti MV, Lavoratti G, Materassi M, Pela I. Hemolytic uremic syndrome: epidemiological and clinical features of a pediatric population in Tuscany. Kidney Blood Press Res. 2010; 33(5):399-404.

Morado M, Freire Sandes A, Colado E, Subirá D, Isusi P, Soledad Noya M et al. Diagnostic screening of paroxysmal nocturnal hemoglobinuria: Prospective multicentric evaluation of the current medical indications. Cytometry B Clin Cytom. 2017; 92(5):361-370.

Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology. 2021; 96(3):114-122.

Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010; 5(10):1844-1859.

Noris M and Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 361(17):1676-1687.

Oh SJ. Muscle-specific receptor tyrosine kinase antibody positive myasthenia gravis current status. J Clin Neurol. 2009; 5(2):53-64.

Pace D and Pollard AJ. Meningococcal disease: clinical presentation and sequelae. Vaccine. 2012; 30 (Suppl 2):B3-9.

Pallaver F, Riviera AP, Piffer S, Ricciardi R, Roni R, Orrico D et al. Change in myasthenia gravis epidemiology in Trento, Italy, after twenty years. Neuroepidemiology. 2011; 36(4):282-287.

Papp V, Iljicsov A, Rajda C, Magyari M, Koch-Henriksen N, Petersen T et al. A population-based epidemiological study of neuromyelitis optica spectrum disorder in Hungary. E J Neurol. 2020; 27(2):308-317.

Papp V, Magyari M, Aktas O, Berger T, Broadley SA, Cabre P et al. Worldwide Incidence and Prevalence of Neuromyelitis Optica. Neurology. 2021; 96(2):59.

Parker CJ. Paroxysmal nocturnal hemoglobinuria. Curr Opin Hematol. 2012; 19(3):141-148.

Poupart J, Giovannelli J, Deschamps R, Audoin B, Ciron J, Maillart E et al. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology. 2020; 94(15):e1645-e1656.

Rachidi S, Musallam KM, Taher AT. A closer look at paroxysmal nocturnal hemoglobinuria. Eur J Intern Med. 2010; 21(4):260-267.

Rafiq A, Tariq H, Abbas N, Shenoy R. Atypical hemolytic-uremic syndrome: a case report and literature review. Am J Case Rep. 2015; 16:109-114.

Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010; 23(4):740-780.

Reiss UM, Schwartz J, Sakamoto KM, Puthenveetil G, Ogawa M, Bedrosian CL et al. Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. Pediatr Blood Cancer. 2014; 61(9):1544-1550.

Richards SJ, Painter D, Dickinson AJ, Griffin M, Munir T, Arnold L et al. The incidence and prevalence of patients with paroxysmal nocturnal haemoglobinuria and aplastic anaemia PNH syndrome: A retrospective analysis of the UK's population-based haematological malignancy research network 2004-2018. Eur J Haematol. 2021; 107(2):211-218.

Risitano AM, Marotta S, Ricci P, Marano L, Frieri C, Cacace F et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: Time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. Front Immunol. 2019; 10:1157.

Ross SC and Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984; 63(5):243-273.

Röth A, Hock C, Konik A, Christoph S, Dührsen U. Chronic treatment of paroxysmal nocturnal hemoglobinuria patients with eculizumab: safety, efficacy, and unexpected laboratory phenomena. Int J Hematol. 2011; 93(6):704-714.

Royston M, Kielhorn A, Weycker D, Shaff M, Houde L, Tanvir I et al. Neuromyelitis Optica Spectrum Disorder: Clinical Burden and Cost of Relapses and Disease-Related Care in US Clinical Practice. Neurol Ther. 2021; 10(2):767-783.

Sahin F, Ozkan MC, Mete NG, Yilmaz M, Oruc N, Gurgun A et al. Multidisciplinary clinical management of paroxysmal nocturnal hemoglobinuria. Am J Blood Res. 2015; 5(1):1-9.

Sakurai M, Jang JH, Chou WC, Kim JS, Wilson A, Nishimura JI et al. Comparative study on baseline clinical characteristics of Asian versus non-Asian patients with paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2019; 110(4):411-418.

Salvadori M and Bertoni E. Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations. World J Nephrol. 2013; 2(3):56-76.

Santos E, Coutinho E, Moreira I, Silva AM, Lopes D, Costa H et al. Epidemiology of myasthenia gravis in Northern Portugal: Frequency estimates and clinical epidemiological distribution of cases. Muscle Nerve. 2016; 54(3):413-421.

Schrezenmeier H, Röth A, Araten DJ, Kanakura Y, Larratt L, Shammo JM et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. Ann Hematol. 2020; 99(7):1505-1514.

Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007; 18(8):2392-2400.

Sheerin NS, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. QJM. 2016; 109(1):27-33.

Sherman E and Han MH. Acute and chronic management of neuromyelitis optica spectrum disorder. Curr Treat Options Neurol. 2015; 17(11):48.

Silvestri NJ and Wolfe GI. Treatment-refractory myasthenia gravis. J. Clin. Neuromuscul. Dis. 2014; 15(4):167-178.

Socié G, Mary JY, de Gramont A, Rio B, Leporrier M, Rose C et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet. 1996; 348(9027):573-577.

Socie G, Schrezenmeier H, Muus P, Lisukov I, Roth A, Kulasekararaj A et al. Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry. Intern Med J. 2016; 46(9):1044-1053.

Souayah N, Nasar A, Suri MF, Kirmani JF, Ezzeddine MA, Qureshi AI. Trends in outcomes and hospitalization charges among mechanically ventilated patients with myasthenia gravis in the United States. Int J Biomed Sci. 2009; 5(3):209-214.

Stellmann JP, Krumbholz M, Friede T, Gahlen A, Borisow N, Fischer K et al. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. J Neurol Neurosurg Psychiatry. 2017; 88(8):639-647.

Sullivan M, Erlic Z, Hoffmann MM, Arbeiter K, Patzer L, Budde K et al. Epidemiological approach to identifying genetic predispositions for atypical hemolytic uremic syndrome. Ann Hum Genet. 2010; 74(1):17-26.

Tomschik M, Hilger E, Rath J, Mayer EM, Fahrner M, Cetin H et al. Subgroup stratification and outcome in recently diagnosed generalized myasthenia gravis. Neurology. 2020; 95(10):e1426-e1436.

Trebst C, Jarius S, Berthele A, Paul F, Schippling S, Wildemann B et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. 2014; 261(1):1-16.

van Deuren M, Brandtzaeg P, van der Meer JWM. Update on meningococcal disease with emphasis on pathogenesis and clinical management. Clin Microbiol Rev. 2000; 13(1):144-166.

Villegas A, Núñez R, Gaya A, Cuevas-Ruiz MV, Bosch JM, Carral A et al. Presence of acute and chronic renal failure in patients with paroxysmal nocturnal hemoglobinuria: results of a retrospective analysis from the Spanish PNH Registry. Ann Hematol. 2017; 96(10):1727-1733.

Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther. 2013; 11(6):597-604.

Westerberg E and Punga AR. Epidemiology of Myasthenia Gravis in Sweden 2006-2016. Brain Behav. 2020; 10(11):e01819.

Westerberg E and Punga AR. Mortality rates and causes of death in Swedish Myasthenia Gravis patients. Neuromuscul Disord. 2020; 30(10):815-824.

Westra D, Volokhina E, van der Heijden E, Vos A, Huigen M, Jansen J et al. Genetic disorders in complement (regulating) genes in patients with atypical haemolytic uraemic syndrome (aHUS). Nephrol Dial Transplant. 2010; 25(7):2195-2202.

Yeh J-H, Kuo H-T, Chen H-J, Chen Y-K, Chiu H-C, Kao C-H. Higher risk of myasthenia gravis in patients with thyroid and allergic diseases: a national population-based study. Medicine. 2015; 94(21):e835-e835.

Yu F, Du Y, Han B. A comparative analysis of clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria between Asia and Europe/America. Int J Hematol. 2016; 103(6):649-654.

Zimmerhackl LB, Besbas N, Jungraithmayr T, van de Kar N, Karch H, Karpman D et al. Epidemiology, clinical presentation, and pathophysiology of atypical and recurrent hemolytic uremic syndrome. Semin Thromb Hemost. 2006; 32(2):113-120.

Signature Page for VV-PVG-001522 v3.0

eSignature Approval	Anne Lappereau-Gallot Other 08-Apr-2025 04:45:29 GMT+0000

Signature Page for VV-PVG-001522 v3.0