EU RISK MANAGEMENT PLAN FOR ZILBRYSQ (ZILUCOPLAN)

40MG/ML, SOLUTION FOR INJECTION (PRE-FILLED SYRINGE)

Version 0.4

Date: 15 Sep 2023 20230915-rmp-v0.4-rtn-003678

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 0.4

Data lock point for this RMP: 31 Mar 2022

Date of final sign off: 15 Sep 2023

Rationale for submitting an updated RMP: Not applicable for initial marketing authorization application submission.

Summary of significant changes in this RMP: Initial marketing authorization application submission – the EU RMP has been updated following the Rapporteurs Day 195 Joint Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) response assessment report.

Major changes consist in:

- Updated Part II Module s2 (developmental and reproductive toxicity) in line with proposed updated EU Summary of Product Characteristics (SmPC).
- Safety concerns: No change.
- Pharmacovigilance plan: No change.
- Risk minimizations:
  - Revision of the Patient Alert Card key messages in Part VII Annex 6.
- Annexes: Update of Annexes 6 and 8.

Other RMP version under evaluation: Not applicable

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

QPPV signature: Please see the electronic signature of the European Economic Area (EEA) QPPV or his deputy on the last page of this module.

Approval Signatures

Name: eu-rmp-rev2-administrative

Version: 8.0

Document Number: PVG-000031363

Title: eu-rmp-rev2-administrative

Approved Date: 15 Sep 2023

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: EEA QPPV Date of Signature: 15-Sep-2023 12:02:20 GMT+0000

Table of Contents

LIST OF ABBREVIATIONS

AChR	acetylcholine receptor
AHR	adjusted hazard ratio
ALS	amyotrophic lateral sclerosis
ATC	Anatomical Therapeutic Chemical
C5	complement component 5
CAP	controlled access program
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
EEA	European Economic Area
EPAR	European Public Assessment Report
gMG	generalized myasthenia gravis
HCP	healthcare professional
IMNM	immune-mediated necrotizing myopathy
IVIg	intravenous immunoglobulin
MAH	marketing authorization holder
MG	myasthenia gravis
PASS	postauthorization safety study
PL	package leaflet
PLEX	plasma exchange
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person for Pharmacovigilance
RMM	risk minimization measure
RMP	risk management plan
SC	subcutaneous(ly)
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics

PART I: PRODUCT OVERVIEW

Table 1: Product overview

Active substance(s)	Zilucoplan
Pharmacotherapeutic group(s)	Immunosuppressants, complement inhibitors, ATC code: L04AJ06
Marketing Authorization Applicant	UCB Pharma S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Zilbrysq
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class**: 15-amino acid, synthetic macrocyclic peptide
	Summary of mode of action: zilucoplan targets C5, a component of the terminal complement activation pathway. Zilucoplan binds to C5 with high affinity and prevents its cleavage by C5 convertases into the cleavage products C5a and C5b. Inhibition of C5 cleavage prevents the downstream assembly and cytolytic activity of the MAC which is involved in the pharmacology of myasthenia gravis disease process. Zilucoplan binds to the domain of C5 that corresponds to C5b. Should any C5b be generated, it will be blocked from binding to C6 by zilucoplan, thereby preventing the subsequent assembly of the MAC (C5b-9).
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labeling and Package Leaflet
Indication(s) in the EEA	Current: Zilucoplan is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR antibody positive.
	Proposed: Not applicable

Table 1: Product overview

<table>
<tr><td>Dosage in the EEA</td><td>Current:
The recommended dose is 0.3mg/kg, given as a subcutaneous injection once daily.
The recommended dose should be given as a subcutaneous injection once daily and administered about the same time every day.
The total daily dose of zilucoplan per body weight range is as follows:
<table>
<tr><th>Body weight</th><th>Dose</th><th>Number of pre-filled syringe by color</th></tr>
<tr><td><56kg</td><td>16.6mg</td><td>1 (rubine red)</td></tr>
<tr><td>≥56 to <77kg</td><td>23.0mg</td><td>1 (orange)</td></tr>
<tr><td>≥77kg</td><td>32.4mg</td><td>1 (dark blue)</td></tr>
</table>
</td></tr>
<tr><td></td><td>Proposed:
Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strength(s)</td><td>Current:
Solution for injection in a pre-filled syringe. One mL contains 40mg of zilucoplan. There are 3 different dose presentations:
0.416mL containing zilucoplan sodium equivalent to 16.6mg of zilucoplan (rubine red pre-filled syringe)
0.574mL containing zilucoplan sodium equivalent to 23mg of zilucoplan (orange pre-filled syringe)
0.810mL containing zilucoplan sodium equivalent to 32.4mg of zilucoplan (dark blue pre-filled syringe)</td></tr>
<tr><td></td><td>Proposed:
Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

AChR=acetylcholine receptor; ATC=Anatomical Therapeutic Chemical; C5=complement component 5; EEA=European Economic Area; gMG=generalized myasthenia gravis; MAC=membrane attack complex; RMP=risk management plan; SmPC=summary of product characteristics

PART II: SAFETY SPECIFICATION

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

1 MYASTHENIA GRAVIS

Based on clinical, epidemiological, immunological, and genetic findings and thymus pathology, MG can be subclassified. Pure ocular MG is distinguished from generalized MG (gMG). Generalized MG is subdivided into early onset (≤50 years) and late onset (>50 years) (Mukharesh and Kaminski, 2019). Early onset MG is often associated with lymphofollicular hyperplasia of the thymus, and late onset MG is characterized by age-dependent involution of the thymus. Approximately 10–15% of all patients have thymoma (thymoma-associated MG) (Melzer et al, 2016).

Approximately 80% of patients with MG are acetylcholine receptor (AChR) antibody positive (Howard, 2018).

1.1 Incidence

Published literature suggests that the incidence rate of MG (all subtypes) varies with age, gender, and ethnic groups (Meriggioli and Sanders, 2009). Estimates of incidence range from 0.3 to 2.8 per 100,000 person years worldwide. In European countries, the annual incidence rate reported ranges from 0.4 (Norway) to 2.1 (Italy) per 100,000 person years (Deenen et al, 2015). In a recent study using primary care data from the Clinical Practice Research Datalink (CPRD), incidence of MG in the UK between 2015 and 2019, was 2.46 per 10,000 (95% confidence interval [CI] 2.34-2.59) (Carey et al, 2021).

1.2 Prevalence

Published epidemiological studies indicate that the estimated prevalence of MG (all subtypes) in the EU is around 2.61 per 10,000 persons (95% CI 2.56.2.68) (zilucoplan UCB Orphan Drug Application, 2021).

The prevalence estimate has been calculated, prioritizing more recent studies over studies that allow for age and sex standardization. The studies included reported prevalence for the period from 2010 until 2020 and incorporated data from Sweden (Westerberg and Punga, 2020), Latvia (Zieda et al, 2018), Spain (Aragonès et al, 2017), Portugal (Santos et al, 2016), Slovakia (Martinka et al, 2018), and Sweden (Fang et al, 2015). The prevalence ranged from 1.12 per 10,000 persons in Portugal to 3.61 per 10,000 persons in Sweden (Westerberg and Punga, 2020). Prevalence estimates of MG from a recent study using primary care data from CPRD in the UK, calculated on 01 Jan 2019, was 3.37 per 10,000 (95% CI 3.27-3.47) (Carey et al, 2021).

1.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The incidence of MG increases with age, therefore the disease is most prevalent in those of older age (Carr et al, 2010). Most studies show MG incidence increasing for men with the peak at the 60-80 years age band, while in women MG incidence appears to have a bimodal age distribution with a peak at 20-40 years then again at 50-70 years (Carr et al, 2010; McGrogan et al, 2010).

A study using the US Nationwide Inpatient Sample found that in the US between 2000 and 2005, black women had a higher adjusted incidence rate of MG when compared to black men, white women and white men (Alshekhlee et al, 2009).

Family history of systemic lupus erythematosus (SLE) was found to be associated with an increased risk of gMG in a study using the Taiwan National Health Insurance Research Database (Kuo et al, 2015). Another study in the same database found that risk of gMG was higher in patients with allergic conjunctivitis, allergic rhinitis, Hashimoto's thyroiditis, Graves' disease and diabetes mellitus (Yeh et al, 2015).

1.4 Main existing treatment options

1.4.1 Existing treatment methods

Myasthenia gravis is a heterogeneous disease which is reflected by numerous disease subcategories that must be considered based on presence or absence of autoantibodies (AChR-MG, muscle-specific kinase-MG, sero-negative-MG), weakness distribution (ocular MG, gMG), age at onset (childhood MG, early-and late-onset MG), and thymus histology (thymoma, non-thymoma), and thus no single treatment approach is suited for all patients. Recently completed clinical studies in MG differ in study design by severity of disease, treatment duration, primary endpoints, steroid tapering protocols, the principal analytic approach, and often contain too narrow eligibility criteria making generalization of study results difficult (Benatar et al, 2018). In the relative absence of evidence from controlled randomized clinical studies (Mantegazza et al, 2011) and no internationally accepted standard of care in MG, various MG treatment guidelines were recently published.

An "International consensus guidance for management of myasthenia gravis" (Sanders et al, 2016) was developed following appointment of a task force of 15 international experts by the Myasthenia Gravis Foundation of America in Oct 2013. In Feb 2019, all previous recommendations were reviewed and new consensus recommendations were developed on topics that required inclusion or updates based on the recent literature (Narayanaswami et al, 2021). The European Federation of Neurological Societies published "Guidelines for treatment of autoimmune neuromuscular transmission disorders" (Skeie et al, 2010). Also, national recommendations for MG treatment have recently been issued by neurological societies, eg, recommendations from the Association of British Neurologists (Sussman et al, 2015), the German Neurological Society (Melzer et al, 2016) and Italian recommendations for the diagnosis and treatment of MG (Evoli et al, 2019).

Treatment approaches for MG can be classified into the following categories (Mantegazza et al, 2011):

- Symptomatic therapy: drugs that immediately improve neuromuscular transmission: acetylcholinesterase inhibitors, eg, pyridostigmine.
- Immunomodulating/immunosuppressing therapies interfering with a number of different disease-causing pathways:
  - Rapid onset of action (within 2 weeks): plasma exchange (PLEX) and intravenous immunoglobulin (IVIg)

  - Intermediate-term onset of action (within 1 to 3 months): corticosteroids, cyclosporine, tacrolimus (FK506), cyclophosphamide, eculizumab
  - Long-term onset of action (up to 1 year and longer): azathioprine, mycophenolate mofetil, rituximab
- Surgical treatment: thymectomy for MG treatment: onset of full efficacy can take several years.
- Generally, the choice of one or more of the immunomodulatory/immunosuppressing agents will be effective in many of the patients with MG. Moreover, side-effects of existing therapies (most of them used off-label) represent an additional challenge. Careful consideration of the benefits and risks for the individual patient and the urgency of treatment defines the short-term, intermediate-term, and long-term treatment objectives. Special treatment considerations in adult patients are to be taken for the patient in "crisis", the "refractory" patient, and for female patients and their partner in case of pregnancy or planning of pregnancy.

1.4.2 Products approved for the treatment of MG (EU)

Table 1–1 presents the products authorized for the treatment of MG in the EU as of the cut-off date of this EU RMP (ie, 31 Mar 2022).

Table 1–1: Products approved for the treatment of MG (EU) as of the cut-off date of 31 Mar 2022

Drug name (Trade name)	Marketing authorization holder	Authorized indication
Cholinergic agents		
Pyridostigmine bromide (Mestinon®)	Mylan Products Ltd	MG
Neostigmine bromide	Alliance Pharmaceuticals Ltd	MG
Distigmine bromide (Ubretid®)	Takeda	MG
Neostigmine methylsulfate (Prostigmine®)	Hameln Pharmaceuticals Ltd; Meda Pharma	MG
Atropine sulphate	Concordia International	In the treatment of cholinergic crisis of MG[a]
Immunomodulating treatment		
Glucocorticoids and other immunosuppressive products		
Prednisolone (Decortin® H)	Merck Serono GmbH	Certain forms of muscle paralysis (MG) (azathioprine being the first choice)
Azathioprine (Imurek®)	Aspen Pharma Trading Ltd	gMG
Biologics		

Table 1–1: Products approved for the treatment of MG (EU) as of the cut-off date of 31 Mar 2022

Drug name (Trade name)	Marketing authorization holder	Authorized indication
Eculizumab (Soliris®)	Alexion Pharmaceuticals, UK Ltd	Refractory gMG in patients who are AChR antibody-positive

AChR=acetylcholine receptor; gMG=generalized myasthenia gravis; MG=myasthenia gravis
[a] Cholinergic crisis results from an overdose of acetylcholinesterase inhibitors

Since the cut-off date of this EU RMP, efgartigimod alpha and ravulizumab were granted a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for marketing authorization on 23 Jun 2022 and 21 Jul 2022, respectively.

1.4.3 Products used off-label for the treatment of MG (EU)

Several immunosuppressants including biologics are used off-label for the treatment of MG, eg, rituximab (MabThera®), cyclophosphamide, ciclosporin, methotrexate, mycophenolate mofetil, and tacrolimus.

In addition, rapid immunomodulating therapies (IVIg and PLEX) are used off-label for the treatment of MG (Janzen, 2018).

1.5 Natural history of the indicated condition in the population, including mortality and morbidity

Myasthenia gravis may be divided into 2 clinical subtypes, ocular and gMG: in ocular myasthenia, the weakness is limited to the eyelids and extraocular muscles; in the generalized disease, the weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

The majority of MG patients present with diplopia and/or ptosis (approximately 85%) and 15% with bulbar symptoms, including dysarthria, dysphagia, and dyspnea. Dysphagia may cause coughing and choking during and after meals, and chewing fatigue is common. Approximately 10% of patients will present with limb or neck weakness. The hallmark symptom of MG is fluctuating and fatigable weakness that is worse at the end of the day and during or following exertion, and improves with rest. Patients may develop a flaccid dysarthria that worsens with prolonged talking. Isolated respiratory failure has been reported in 1% of patients. Myasthenia gravis symptoms are exacerbated by heat, stress, infection, a variety of drugs, and rarely vaccines (Gwathmey and Burns, 2015). Ocular symptoms are the first and sole manifestation in about 50% of patients. Of these patients, 50-80% progress to develop gMG, usually within 2 years (Gilhus et al, 2019).

During the natural course of MG, it is estimated that 57% of patients experience general improvement, and remission is seen in 13% of patients after the first 2 years.

Risk factors for progression to generalized disease include adult-onset ocular MG, abnormal repetitive nerve stimulation findings, thymoma (Guo et al, 2021) and seropositivity for AChR antibodies (Guo et al, 2021; Kemchoknatee et al, 2021). Several studies have reported increased MG severity in women than in men (Boscoe et al, 2019; Engel-Nitz et al, 2018), including a

recent cohort study of 70 patients followed over 7 years and using objective and patient-reported outcome measures (Thomsen et al, 2021). Significant progress has been made in the last 2 decades around our understanding of the disease, leading to new treatment modalities and a significant reduction in morbidity and mortality. However, although a high proportion of patients respond well to conventional treatment, drug-free remission is rare, chronic immunosuppression is usually needed, and 10-15% of patients have refractory disease (Schneider-Gold et al, 2019). Moreover, severe weakness symptoms can be accompanied by higher mortality; 20% of patients remain unchanged, with mortality from the disease of 5–9% (Dresser et al, 2021; Grob et al, 2008). If not adequately treated, gMG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. This can potentially lead to the most dangerous complication of gMG, known as myasthenic crisis, requiring hospitalization, intubation, and mechanical ventilation. Up to 20% of patients with gMG will experience a myasthenic crisis, 75% of them within 2 years of diagnosis (Shanker and Ramizuddin, 2014).

1.5.1 Mortality

A study in Denmark compared 702 patients with AChR positive MG diagnosed between 1985 and 2005, and followed up until 2009, with an age and sex matched cohort of 7020 patients without MG, and found an overall adjusted mortality rate ratio of 1.41 (95% CI 1.24–1.60). Mortality was highest in the 5 years following onset of MG (Hansen et al, 2016).

A systematic review of 8 studies carried out between 1950 and 2007 showed a range in mortality rates due to MG from 0.06 - 0.89 per million person-years (Carr et al, 2010). Cardiovascular disease and malignancy are the most common causes of death in patients with MG, as is the case in the general population (Christensen et al, 1998).

The Nationwide Inpatient Sample study carried out in the US between 2000 and 2005, estimated the in-hospital mortality rate to be 2.2% in MG patients in general, and 4.5% for those admitted with myasthenic crisis. Independent risk factors for mortality in this population were age, diagnosis of myasthenic crisis and respiratory failure requiring intubation (Alshekhlee et al, 2009).

One US study of 1976 patients with MG found that mortality from MG decreased progressively during 1958–2000 compared to 1940–1957. The mortality rate has been consistently, but not significantly, higher in males (14%) than females (11%). The mean duration of MG at the time of death increased from 4.8 to 5.9 years during 1940–1965 to 10.3 to 8.6 years during 1966–2000. This duration did not differ significantly between males and females at any time point. The age of patients who died of MG increased significantly during 1966–2000 compared to 1940–1965 in both sexes (Grob et al, 2008).

1.5.2 Morbidity

A systematic review including 27 retrospective studies, provided evidence of an initial MG exacerbation following corticosteroid treatment (Lotan et al, 2021). The highest rates were found for cortisone administration and the lowest rates for methylprednisolone. Thirty-one percent of events with reported severity of initial exacerbation were classified as mild or moderate and only 7% as severe. Fourteen percent of the total episodes of clinical worsening were mild or severe and for 6% of total events, reduction in muscle strength was severe. Risk factors for initial exacerbation were administration of high daily dose or alternate day prednisolone, older age,

gMG, bulbar symptoms, MG severity, presence of thymoma and thymectomy. However, methodology and treatment (eg, frequency and dose) were highly heterogeneous across studies and there was a lack of appropriate comparators and adjustment for confounding. Treatment for MG can increase the risk of coexisting disorders. Prednisolone necessitates prophylaxis against osteoporosis, and patients should be monitored for weight gain, elevations in blood glucose levels, and hypertension. A recent single center study in the USA, based on the medical review of charts from patients with gMG treated with oral corticosteroids for ≥1 year, reported a median number of corticosteroid-related adverse side effects of 2 per patient (Johnson et al, 2021). Side effects were more common in patients treated with >30mg/day prednisone (compared to ≤30mg/day). Pre-diabetes and weight gain were the most common. Weight gain and irritability were more prevalent in women and osteoporosis and pre-diabetes in men. Anticholinergic drugs for symptomatic treatment have transient and dose-limiting effects on the autonomic nervous system most often involving the gastro-intestinal tract (eg, diarrhea, abdominal pain or cramps) as well as urinary urgency and increased sweating (Gilhus et al, 2016).

1.6 Important comorbidities

There are a number of comorbidities which occur at a higher rate in patients with MG, and these represent a major challenge for MG patients. Comorbidity may be crucial for quality of life, daily functions, short-term and long-term outcome, and even mortality (Gilhus et al, 2015). Presence of risk factors for comorbidities, MG complications, and treatment side effects constitute the major mechanisms for additional health impairment in MG. Patients with gMG and comorbidities have a poorer prognosis than patients with MG alone (Laasko et al, 2021). The risks of the medicinal product are evaluated based on the characteristics of the medicinal product (eg, documented in clinical trials) and the context of use: expected comorbidities and co-medications in the target population. Patients with unexpected deterioration, lack of therapeutic response or new symptoms/signs should always be examined for comorbidity. Common comorbidities found in MG patients include:

- Other autoimmune disease: amongst patients with MG, it is estimated that approximately 15% of patients have a second autoimmune disease (Gilhus et al, 2015), which occurs most frequently in patients with early-onset MG and thymic hyperplasia. Thyroid disease is the most common coexisting condition, followed by SLE and rheumatoid arthritis. Type 1 diabetes is also common. In a study conducted in a referral center in Mexico, abnormal thyroid function testing was found in 19% of MG patients, 13% presented hypothyroidism and 6% hyperthyroidism (Cacho-Diaz et al, 2015). In this cohort of patients with MG, 98% of patients with dysthyroidism had a generalized form of MG. Neuromyelitis optica with aquaporin-4 has a specific association with MG and can occur either before or after the onset of MG.
- Respiratory disease: a study over several decades has reported 39% of patients with MG had reduced vital capacity, and 19% of those with severe gMG experienced an MG crisis with a need of assisted ventilation. However, mortality during MG crisis has been reduced to approximately 4%, and in well treated MG populations there is no longer increased mortality due to respiratory disease (Gilhus et al, 2015).
- Malignancy: immune-mediated diseases, including MG, may increase a risk for carcinogenesis in general. According to the UK Biobank study, any immune-mediated

disease was related to a modestly increased risk of total cancer, with a hazard ratio of 1.08 (95% CI: 1.04-1.12) (He et al, 2022). Thymomas (MG thymoma) seem to have an increased risk (standardized incidence ratio 1.94, 95%CI: 1.29-2.81) (Filosso et al, 2013) for some cancer types such as lymphoma (Gilhus et al, 2015; Gilhus and Verschuuren, 2015). A cohort study from Taiwan comprising 2614 MG patients reported a higher risk of extrathymic cancers with an incidence rate ratio of 1.38 (95% CI: 1.12-1.68) compared with matched controls without MG after an average follow-up of 8 years (Liu et al, 2012). In addition, a Swedish cohort study showed that 22.4% of the 2812 included MG patients developed extrathymic cancer (Verwijst et al, 2021). Immunosuppressive drugs may alter the immune system's ability to detect and destroy cancer cells or fight off infection (eg, Epstein-Barr virus) which cause cancer such as lymphomas (NCI 2015). The longterm use of immunosuppressants like azathioprine, which is used in MG treatment management and a variety of other immune-mediated diseases, may result in impaired immune surveillance with potential to increase cancer risk (Zhang et al, 2021; Gilhus and Verschuuren, 2015). A systematic review and meta-analysis showed that MG patients receiving azathioprine may be associated with a slight increase (odds ratio 1.09; 95%CI 0.86-1.38) in developing cancer (Zhang et al, 2021). Based on the available data on immunosuppression, patients with immune-mediated conditions taking certain immunosuppressants, like methotrexate (15% increased risk of melanoma) or alkylating agents (a 3-fold higher incidence of nonmelanoma skin cancer [Heijl et al, 2011]) may benefit from regular skin cancer screening (Kreher et al, 2023).

Evidence from observational and clinical trials has identified no significant increased risk of cancer overall associated with of certain biologics, including anti-TNF and rituximab (Xie et al, 2020).

- Heart disease: cardiomyositis may occur more often in MG than in other autoimmune disorders. In population-based studies, patients with MG do not have more frequent heart disease or heart disease mortality. However, autonomic function tests of the heart in patients with MG have shown instability in the sympathetic or parasympathetic systems (Gilhus et al, 2015).
- Nervous system disorder: patients with thymoma MG have an increased risk for autoimmune encephalitis. Registry-based studies report a relationship between autoimmune disease and schizophrenia. Amyotrophic lateral sclerosis (ALS) occurs in patients with MG more often than would be expected based on the risk in the general population (Gilhus et al, 2016). In a registry-based study, MG was reported in 36 patients with ALS compared with an expected number of 7.2 (Gilhus et al, 2015).
- Diabetes: findings from a registry-based population study conducted in Norway showed that insulin treatment was prescribed almost 3 times more often in patients with MG than in the general population (Andersen et al, 2014). In a study conducted in a referral center in Mexico, diabetes mellitus was diagnosed in 20% of patients with MG (Cacho-Diaz et al, 2015).
- Dyslipidemia: in the Oxford Myasthenia Centre registry, hypercholesterolemia was amongst the most common comorbidities in MG and prevalence was higher in patients with late onset MG than in those with early onset (41.2% vs. 23.8%) (Klimiec-Moskal et al, 2021). In a

referral center in Mexico, dyslipidemia was diagnosed in 60% of patients with MG (Cacho-Diaz et al, 2015). A recent study in Taiwan (Chu et al, 2019) compared 349 MG patients with 1396 age-sex matched non-MG individuals and found that dyslipidemia was among comorbidities that was higher in the MG patients than in control patients (26.1% vs. 15.8%).

- Osteoporosis: this is a progressive bone disease characterized by low mineral density and microarchitectural deterioration of bone tissue. These abnormalities lead to an increased risk of fragility fracture. Osteoporosis is a common adverse effect of long-term oral corticosteroids, which is often used for the management of MG patients. It is also more common in postmenopausal women, men over 50 years and individuals with rheumatoid arthritis and diabetes. A recent study based on linkage of national registries in Denmark found no increased frequency of major osteoporotic fracture in patients with MG (Safipour et al, 2021). A previous population-based study conducted in the UK had also found that the risk of any fracture and osteoporotic fracture did not differ between individuals with MG and age- and sex-matched controls irrespective of corticosteroid use (Pouwels et al, 2013). Effective prophylaxis against osteoporosis is important and might explain the reason for few fractures (Gilhus et al, 2015).
- Depression and anxiety: depression and anxiety can occur in MG patients, combined with a reduced health-related quality of life. A review of psychiatric comorbidity in patients with MG, reported that one third of patients have depression, and up to 46.3% are diagnosed with an anxiety disorder (Law et al, 2020). Risk factors for depression were longer MG disease duration, disease severity, and MG-induced respiratory failure. Treatments with hypnotics, sedatives and antidepressant drugs were 1.2-1.5 as common in an national MG population compared with controls in Norway (Andersen et al, 2014).
- Hypertension: in a study based on the analysis of the Oxford Myasthenia Centre registry, hypertension was the most common comorbidity in MG patients (up to 58.4% in late onset MG) (Klimiec-Moskal, 2021). While the prevalence of arterial hypertension has been found to be lower in MG than in the general population, the use of corticosteroids and the number of emergency visits in patients with hypertension was higher in patients with than without MG (Cacho-Diaz et al, 2015).
- Infection: 3 factors may increase the risk of infection in people with MG: muscle weakness, autoimmune disease mechanism, and immunosuppressive treatment (Gilhus et al, 2018). First, higher risk of lower respiratory infections may result from weakness in the respiratory muscles or from aspiration pneumonia caused by dysphagia. Pelvic muscle weakness might also increase the risk of urinary tract infections. Second, thymus disorder or thymectomy could also predispose to infections or to infection severity. Third, MG patients often receive prolonged treatment with and high doses of immunosuppressive drugs, which can also increase the risk of infection. Two longitudinal studies compared the incidence of infection between the MG and the general population. Kassardjian et al (2020) conducted a population-based cohort study in Ontario, Canada, in the period between Apr 2002 and Dec 2015 (Kassardjian et al, 2020). The study used linked health administrative data and included 3823 patients with MG and 15,292 comparators from the general population, matched for age, sex and region of residence. Over a mean of 5.4 (standard deviation [SD] 3.8) years, a 39% increased risk of severe infection (ie, primary diagnosis on hospital or emergency records) was found for MG (72.5 vs 35.0 per 1000 person-years; adjusted hazard

ratio [AHR] of 1.39, 95% CI 1.28-1.51). The most common types of infections diagnosed in MG patients were all-cause respiratory infections (21.6%), bacterial pneumonia (15.8%), skin/soft tissue infections (9.6%), and septicemia (6.7%). Risk factors for infection amongst MG patients were rurality, chronic obstructive pulmonary disease (COPD), hypertension, prior infection, frailty, and comorbidity burden. The second longitudinal study used the Taiwan National Health Insurance database to compare the incidence of tuberculosis between 2317 patients with MG and 23,170 age-, sex- and comorbidity-matched controls (Ou et al, 2013). The study period was between 2000 and 2006 and the median follow-up over 3 years. Incidence of tuberculosis was higher in MG than in the comparator group (29.2 vs. 13.3 per 10,000 person-years; AHR of 1.96, 95% CI 1.22-3.16) and most patients had pulmonary tuberculosis. Risk factors for tuberculosis amongst MG patients were, an age of 60 or more and use of corticosteroids. Presence of thymoma, prior thymectomy, diabetes mellitus, or COPD did not increase tuberculosis risk. Sipila et al. investigated hospitalization trends in MG patients between 2004 and 2014, using the national registry of Finland (Sipila et al, 2019). Eight hundred and sixty-one MG patients had a total of 2989 hospital admissions and the proportion of infections as the primary diagnosis increased from 4.5% to 10.4% during the study period. The most common diagnoses were lower respiratory tract infections (N=65/240, 27.1%), septicemia (N=36/240, 15%), and urinary tract infections (N=18/240, 7.5%). Finally, a study in China compared the infection rate post-thymectomy, between 53 MG patients with early extubation and 43 patients with late extubation. The authors found a higher risk of postoperative pulmonary infection (39.5% vs. 11.3%, respectively) in patients with late extubation (Chen et al, 2019).

PART II: MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage are presented in Table 1.

A comprehensive toxicology program has been conducted for zilucoplan including a 4-week subcutaneous (SC) repeat-dose toxicology studies in rats and 4-, 13-, and 39- week SC repeat-dose toxicology studies in cynomolgus macaques, reproductive and developmental toxicology studies in cynomolgus macaques, in vitro and in vivo safety pharmacology, and a battery of genotoxicity assays.

Zilucoplan shows similar pharmacological activity in cynomolgus macaque as in human, moderate activity in pigs, very weak in rats (>100 times lower than cynomolgus macaque) and no activity in other species such as mice, guinea pigs, dogs, or rabbits. Based on pharmacological activity, similarity in metabolite profile, and ratio of metabolites to parent drug, the cynomolgus macaque is considered to be the most relevant animal species for toxicology testing.

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
General toxicity	In the pharmacologically relevant cynomolgus macaque, the main finding has been epithelial mononuclear infiltrates and vesicular degeneration with associated secondary sequelae in various locations on the body. In the cervix, the epithelial vesicular degeneration and mononuclear infiltrates were accompanied by increased incidence and severity of squamous metaplasia, and rarely by epithelial erosions. Squamous metaplasia is often noted in animal studies secondary to chronic irritation and can as such be attributed as a secondary sequela. The immunological presentation and degenerative nature are suggestive of a response to antigenic stimulation secondary to pathogen reactivation or de novo infection. Bacterial pathogens (*Staphylococcus aureus*, *Beta hemolytic streptococci*, *Pseudomonas*, and *Enterococcus*) in the early euthanasia animals and parasites (detected by histopathology) in the cecum of some treated animals were identified in the 39-week toxicology study. Additionally, *Balantidium* sp. protozoa was found in the early euthanasia animal with colitis (Animal No 2501). In the 13-week repeat-dose study all fecal samples analyzed via polymerase chain reaction were positive for *Entamoeba*, including controls. Most samples were also positive for parasites by	The type of infections as referenced in the left column and their associated sequelae are not directly translatable to the human as the background microbiome, levels of background/latent infection, stress, hygiene, cross-contamination between macaques, and relative fragility, vastly differs between the species (Olivier et al, 2010). A more detailed analysis of skin infections can be found in the Integrated Summary of Safety. Infection-related safety findings in cynomolgus macaques can be highly variable from study to study and have limited ability to accurately predict the incidence and type of infection that can be expected in humans (Martin and Bugelski, 2012; Olivier et al, 2010; Sasseville and Mansfield, 2010; Price, 2010).

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	histopathology in the cecum. Additionally, Animal No. 2002 was also positive for alpha hemolytic *Streptococci* in the Week-13 sample. This confirms the hypothesis that these NHPs had pathogens and it is likely that immunomodulation made the treated NHPs more susceptible to primary outbreaks or recrudescence of these pathogens. The infections seen in NHPs are not considered translatable to humans due to the different microbial flora present on skin, on mucosa, and in the gastrointestinal tract, the different immune status, and the different hygiene/grooming behaviors and environment of the monkeys compared with humans. Although the animals in these studies underwent prescreening for common pathogens (eg, simian retrovirus, simian immunodeficiency virus, measles) and intestinal pathogens (*Giardia, Cryptosporidium, Entamoeba*), challenges in screening primate colonies for latent infections are well recognized (Olivier et al, 2010). As such, besides the identified pathogens, it cannot be excluded other undiscovered pathogens were present and contributed to the findings. Virus infections such as Macacine Herpes Virus-1, which are epitheliotropic and can often be latent and endemic in primate colonies, may manifest lesions such as vesicles or ulcers on mucous membranes during immunosuppression (Wachtman and Mansfield, 2012; Keeble et al, 1958). Such infections and their associated sequelae are not directly translatable to the human. Pancreatic infiltrates and degeneration, lymphoid hypercellularity, and sporadic bridging bile duct hyperplasia and hepatic fibrosis have been observed and the possibility cannot be excluded that these findings were also secondary to pathogen proliferation, colonization, and infection, possibly through secondary ascending infection of the bile duct. In persistently infected animals, lymphoid follicles can appear in a variety of organs - usually the salivary glands, pancreas, kidneys, thymic medulla, and bone marrow (Guzman et al, 1999). But also, liver findings can be a secondary consequence of pathogen infections. *Enterocytozoon bieneusi* is a common	In addition, several viral, bacterial, and parasitic pathogens are endemic in cynomolgus macaques and remain clinically undetectable or are mild and self-limiting in immunocompetent animals (Sasseville and Mansfield, 2010). The difference in infection-related safety findings between humans and cynomolgus macaques is most likely due to the different bacterial flora present on skin, on mucosa, and in the gastrointestinal tract, the different immune status, and the different hygiene/grooming behaviors in monkeys compared with humans. Indeed, these are also likely responsible for the varying infection-related effects observed between individual animals within a study. Such variables are also likely to be responsible for different infection profiles depending on the monkey origin, colony, or contract research organization used for a study. In addition, immunomodulation can make a primate more susceptible to primary outbreaks or recrudescence of these pathogens (Price, 2010; Olivier et al, 2010). In the placebo-controlled pools of gMG/IMNM studies, the overall incidence of laboratory abnormalities of amylase increased and lipase increased were higher in the zilucoplan treatment group compared to placebo. The overall incidence of TEAEs of amylase

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	microsporidian parasite of the gastrointestinal tract of macaques and causes bile duct hyperplasia and bridging hepatic fibrosis if immunosuppressed. Additionally, various reactivated herpes viruses can also infect the hepatobiliary system causing necrosis (Wachtman and Mansfield, 2008). Such infections and their associated sequelae are not directly translatable to the human. Several animals (in the 4-, 13- and, 39-week toxicology studies) presented with abdominal pain/icterus/bile duct hyperplasia/peribiliary inflammation or bridging bile duct hyperplasia and hepatic fibrosis. In the animals of the 13-and 39-week study, clear increases in clinical chemistry biomarkers of cholestatic hepatic injury were observed. The reversibility of these lesions could not be assessed, since the lesions were identified in a recovery group animal in the 13-week study, and in an animal requiring early termination due to skin lesions in the 39-week study. However, the liver enzyme changes observed during the dosing phase of the 13-week study in the animal with microscopic changes in the liver were not observed at the time of recovery euthanasia, showing a trend towards reversibility in the affected animal. Bridging bile duct hyperplasia and hepatic fibrosis were not observed in any of the terminal euthanasia animals or the recovery animals in the 13-week study, nor in the animals surviving to the end of the 39-week repeat-dose toxicology study. In the pancreas, reversible dose- and duration-dependent mononuclear infiltrates were occasionally noted in the 13- and 39-week toxicology studies. Sporadically, minimal to mild exocrine pancreas acinar degeneration was noted in these studies at ≥1mg/kg. These findings were reversible below 10mg/kg. In the 13-week study, sporadic increases in lipase and amylase were observed at 0.25, 2 and 10mg/kg but not at 1mg/kg, with more consistent increases in these enzymes at 10mg/kg. These were accompanied by mononuclear cell infiltrates, were not seen in all animals in each dose group and frequently recovered or returned towards pre-dose levels despite continued treatment. In contrast, in the	increased were slightly higher in the zilucoplan treatment group compared to placebo, whereas there was no difference between groups for the TEAEs of lipase increased. Pancreatic enzyme elevations were generally transient with a variable time-to-onset and resolved over time with continuation of zilucoplan. Lipase elevations were more frequent than amylase elevations. No elevations lead to treatment discontinuations except for one lipase elevation. No evidence suggestive of zilucoplan-induced pancreatitis or other pancreas pathologies was identified. Following a review of all data, and mainly based on the higher incidence of laboratory abnormalities in the zilucoplan treatment group compared to placebo, amylase increased and lipase increased are considered as ADRs for zilucoplan. Based on the inconsistent occurrence between nonclinical studies and considering that the elevated pancreatic enzyme levels are likely secondary to pathogen proliferation and as such not considered translatable to humans, no clear link has been established between the pancreatic enzyme elevations in nonclinical and clinical studies.

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	39-week study, excluding the early euthanasia animals, non-statistically significant minimal to mild increased lipase and amylase were observed only at 4 and 6mg/kg. These changes were generally within the historical and/or study control range, transient and reversible and therefore consistent either with background changes or transient low-grade infections. Overall, these elevations in pancreatic enzymes showed an inconsistent occurrence between studies and the elevated serum concentrations of amylase and lipase recovered or approached recovery despite continued dosing. These could be secondary to pathogen proliferation, which is supported by the fact no consistent elevations in pancreatic enzyme levels were seen in the 13-week male fertility study and the combined EFD/ePPND study (both studies have a duration past the D56-84 peak seen in the affected animals) where epithelial mononuclear infiltrates and vesicular degeneration were also not observed. Lymphoid hyperplasia (described variously as lymphoid hypercellularity, increased lymphoid aggregates or increased lymphoid follicles) were noted in the thymus of the 4, 13, and 39-week cynomolgus macaques studies as well as in the bone marrow and spleen during the 39-week study. In the latter study, lymphoid follicles were described as active secondary follicles indicative of an ongoing immune (B-cell) response. It is possible that this is an adaptive immune response to pharmacologic inhibition of C5 which resulted in immunosuppression and secondary pathogen proliferation, colonization, and infection. Such infections and their associated sequelae are not directly translatable to the human.	
Local tolerance	No separate local tolerance studies have been conducted. However, local tolerance at site of injection was assessed in the repeat-dose cynomolgus macaques and rat studies. Injection site reactions were generally mild and reversible in cynomolgus macaques, while in rats, these reactions were more significant in some high-dose animals which would be in line with the higher doses administered to the rat.	In the clinical Phase 3 studies, fixed amounts of zilucoplan of max 32.4mg will be administered to a 77kg individual. The max expected dose would therefore be 0.42mg/kg. As such there is approximately a 100x safety margin compared to the adverse ISRs seen in the rat.

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	In the cynomolgus macaque, which is the pharmacologically relevant species, ISR were generally mild and reversible. In the rat the adverse ISRs were noted at 40mg/kg.	Additionally, in the clinical studies, ISRs were reported as nonserious events, mild to moderate in severity and generally not leading to product discontinuation.
Developmental and reproductive toxicity	In female reproductive organs (vagina, cervix, uterus), mononuclear cell infiltrates with epithelial degeneration and cervical squamous metaplasia were seen in some repeat-dose toxicity studies. Female animals presenting findings in the reproductive organs also had a similar pattern and spectrum of changes in other organs characterized principally by mononuclear cell infiltrates and epithelial degeneration. The findings in NHPs are possibly related to infections secondary to the pharmacological effect of zilucoplan, but other mechanisms and their clinical relevance cannot be excluded. These findings did not correlate with any effects on embryofetal development or pregnancy outcomes (pregnancy loss, parturition, pregnancy outcomes, or infant post-natal development) in NHPs at similar dose levels. In a monkey male fertility study, minimal to slight germ line degeneration/depletion was observed at clinically relevant exposures but severity did not increase with dose. No impact on spermatogenesis was observed. No developmental or reproductive effects were observed in a combined EFD/ePPND study in pregnant female cynomolgus macaques. An ex-vivo closed-circuit human placental transfer model suggests low transfer rate of zilucoplan (0.5-1.0%) in the fetal compartment. The transfer rate of 0.5% was observed at a steady state plasma concentration of 10µg/mL zilucoplan, corresponding to a therapeutic dose of 0.3mg/kg.	The clinical relevance of the low transfer rate (0.5-1%) seen in the ex vivo human placental transfer model in human pregnancies is unknown.
Genotoxicity	Zilucoplan was not genotoxic when tested in vitro in a bacterial reverse mutation (Ames) study and chromosomal abnormality assay study. In addition, no genotoxic potential was observed in an in vivo rat bone marrow micronucleus assay.	Not relevant
Carcinogenicity	No carcinogenicity studies have been conducted for zilucoplan. A comprehensive assessment of	To date, the continuous review of the clinical safety data from

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	the carcinogenic potential for zilucoplan, its metabolites, and potential impurities has been conducted. Considering that families with C5 deficiencies and mouse strains lacking C5 do not show any evidence of tumorigenicity and that a comprehensive nonclinical program has been conducted on zilucoplan, no further studies in the primate are warranted since they are unlikely to add further understanding to the potential for human risk. Studies in rodents are not feasible for zilucoplan, as it does not cross-react with the mouse and only has very weak activity in rat (>100 times lower than cynomolgus macaque) and data on the mouse strains lacking a functional complement component 5 do not show evidence of increased tumorigenicity.	the zilucoplan development program did not identify any safety signal with respect to malignancies.
Safety pharmacology		
Cardiovascular	No zilucoplan-related effects were seen in a stand-alone cardiovascular and respiratory safety pharmacology study in cynomolgus macaques or in the safety pharmacology assessments in the repeat-dose toxicology studies in the cynomolgus macaque.	Not relevant

ADR=adverse drug reaction; C5=complement component 5; EFD=embryo-fetal development; ePPND=enhanced pre- and postnatal development; gMG=generalized myasthenia gravis; IMNM=immune mediated necrotizing myopathy; ISR=injection site reaction; NHP=non-human primate; TEAE=treatment-emergent adverse event

In conclusion, in some non-human primate repeat-dose toxicity studies, findings of uncertain clinical relevance were observed which were possibly due to infections, but other mechanisms cannot be excluded. In the pharmacologically relevant cynomolgus macaque, the exposure multiples calculated for the pivotal toxicology studies are considered adequate. For the 13- and 39-week toxicology studies 2.0-2.2x safety margins have been calculated and for the embryo-fetal development (EFD)/enhanced pre- and postnatal development (ePPND) and male fertility study 4.3-7.8x safety margins have been calculated. Safety margins were based on both modelling of the predicted exposure of an 80kg patient receiving a 32.4mg dose and based on data from the clinical ethnic bridging study. The exposure multiples calculated from the pivotal toxicology studies are considered adequate and thus the nonclinical program supports marketing authorization of zilucoplan as a once daily, self-administered, SC injection.

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

1 POOL S1B

The purpose of Pool S1B is to present the long-term safety data of zilucoplan 0.3mg/kg, and of all zilucoplan-treated study participants with gMG. This pool combines the safety data (double-blind and open-label) from the following studies:

- gMG Phase 2 study: MG0009 (ie, Main double-blinded and open label Extension Portions)
- gMG Phase 3 study: MG0010 (double-blinded)
- gMG Phase 3 open-label extension study: MG0011

Pool S1B Safety Population includes all study participants who received at least 1 dose of zilucoplan treatment in MG0010, the double-blind Main Portion of MG0009, the Extension Portion of MG0009, or in MG0011. Pool S1B does not include study participants who received placebo in MG0010 or the double-blind Main Portion of MG0009 and discontinued prior to receiving zilucoplan.

Table 1–1 presents the study participant exposure to zilucoplan in Pool S1B by duration of exposure.

Table 1–1: Duration of exposure (Pool S1B) (All zilucoplan)

Duration of exposure	Study participants (%)	Participant-years
≥ 1 day	213 (100)	262.4
≥ 30 days	212 (99.5)	262.3
≥ 60 days	196 (92.0)	260.0
≥ 90 days	186 (87.3)	258.0
≥ 6 months (182 days)	139 (65.3)	239.8
≥ 12 months (365 days)	98 (46.0)	211.2
≥ 18 months (547 days)	57 (26.8)	161.7
≥ 24 months (730 days)	40 (18.8)	132.2
≥ 36 months (1095 days)	32 (15.0)	114.5
≥ 48 months (1460 days)	1 (0.5)	4.2
Total	213 (100)	262.4

Data source: Integrated Summary of Safety Table 4.2.1

Table 1–2 presents study participant exposure to zilucoplan in S1B Pool by age group and gender.

Table 1–2: Exposure by age group and gender (Pool S1B) (All zilucoplan)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<18 years	0	0	0	0
18 to <65 years	59 (27.7)	99 (46.5)	97.2	113.5
65 to <75 years	33 (15.5)	17 (8.0)	24.8	22.2
75 to <85 years	3 (1.4)	2 (0.9)	2.5	2.2
≥ 85 years	0	0	0	0
Total	95 (44.6)	118 (55.4)	124.4	137.9

Data source: Integrated Summary of Safety Table 4.3.1

Table 1–3 presents study participant exposure to zilucoplan in Pool S1B by dose.

Table 1–3: Exposure by dose (Pool S1B)

Dose of exposure	Study participants	Participant-years
Zilucoplan 0.1mg/kg	22	21.6
Zilucoplan 0.3mg/kg	212	240.7
Total	213	262.4

Data source: Integrated Summary of Safety Table 4.2.1

Table 1–4 presents study participant exposure to zilucoplan in Pool S1B by ethnic origin.

Table 1–4: Exposure by ethnic origin (Pool S1B) (All zilucoplan)

Ethnic origin	Study participants (%)	Participant-years
Black or African American	19 (8.9)	29.5
White	159 (74.6)	199.0
Asian	23 (10.8)	24.4
Other	5 (2.3)	3.2
Missing	7 (3.3)	6.4
Total	213 (100)	262.4

Data source: Integrated Summary of Safety Table 4.4.1
Note: Other is defined as any study participant not identified as White, Asian, or Black or African American

2 POOL S2B

The purpose of Pool S2B is to present all available, unblinded, long-term safety data of zilucoplan at any dose (or dose sequence) in all zilucoplan-treated study participants with gMG or immune-mediated necrotizing myopathy (IMNM). This pool combines the safety data (double-blind and open-label) of all study participants who received zilucoplan in the following unblinded Phase 2 and Phase 3 studies across the gMG and IMNM target indications. These target indications are considered to have a similar patient population in terms of age, gender, expected background mortality and adverse event rates.

- gMG Phase 2 study: MG0009 (ie, Main double-blinded and open-label Extension Portions)
- gMG Phase 3 study: MG0010 (double-blinded)
- gMG Phase 3 open-label extension study: MG0011
- IMNM Phase 2 study: IMNM01 (ie, Main and Extension Portions)

Pool S2B is the subset of the data when the study participants were on zilucoplan and excludes the data when the study participants were on placebo. Study participant data from the Phase 3 extension study (MG0011) was programmatically linked to corresponding data collected within the parent Phase 2 (MG0009) or Phase 3 (MG0010) study via each study participant's unique subject number which has been retained from the qualifying study.

The Pool S2B Safety Population includes all study participants who received at least 1 dose of zilucoplan treatment.

Table 2–1 presents the study participant exposure to zilucoplan in Pool S2B by duration.

Table 2–1: Duration of exposure (Pool S2B) (All zilucoplan)

Duration of exposure	Study participants (%)	Participant-years
≥ 1 day	238 (100)	275.2
≥ 30 days	237 (99.6)	275.2
≥ 60 days	221 (92.9)	272.9
≥ 90 days	210 (88.2)	270.6
≥ 6 months (182 days)	151 (63.4)	248.0
≥ 12 months (365 days)	99 (41.6)	212.7
≥ 18 months (547 days)	58 (24.4)	163.2
≥ 24 months (730 days)	40 (16.8)	132.2
≥ 36 months (1095 days)	32 (13.4)	114.5
≥ 48 months (1460 days)	1 (0.4)	4.2
Total	238 (100)	275.2

Data source: Integrated Summary of Safety Data 4.2.2

Table 2–2 presents study participant exposure to zilucoplan in S2B Pool by age group and gender.

Table 2–2: Exposure by age group and gender (Pool S2B) (All zilucoplan)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<18 years	0	0	0	0
18 to <65 years	71 (29.8)	106 (44.5)	103.4	117.3
65 to <75 years	35 (14.7)	21 (8.8)	25.7	24.2
75 to <85 years	3 (1.3)	2 (0.8)	2.5	2.2
≥ 85 years	0	0	0	0
Total	109 (45.8)	129 (54.2)	131.6	143.7

Data source: Integrated Summary of Safety Table 4.3.2

Table 2–3 presents study participant exposure to zilucoplan in Pool S2B by dose.

Table 2–3: Exposure by dose (Pool S2B)

Dose of exposure	Study participants	Participant-time
All zilucoplan	238 (100)	275.2

Data source: Integrated Summary of Safety Table 4.3.2

Table 2–4 presents study participant exposure to zilucoplan in Pool S2B by ethnic origin.

Table 2–4: Exposure by ethnic origin (Pool S2B) (All zilucoplan)

Ethnic origin	Study participants (%)	Participant-years
Black or African American	22 (9.2)	31.0
White	175 (73.5)	207.7
Asian	23 (9.7)	24.4
Other	6 (2.5)	3.6
Missing	12 (5.0)	8.6
Total	238 (100)	275.2

Data source: Integrated Summary of Safety Table 4.4.2
Note: Other is defined as any study participant not identified as White, Asian, or Black or African American

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Exclusion criteria in pivotal clinical studies within the development program are discussed in Table 1–1.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Current or recent systemic infections (including *Neisseria* infections and history of meningococcal disease)	
Reason for exclusion	The mechanism of action of zilucoplan is based on inhibition of complement C5 and the terminal complement pathway. Deficiency of terminal complement components is associated with an increased incidence of infection with *Neisseria* species, in particular *Neisseria meningitidis*, as *Neisseria* bacteria are primarily cleared by the terminal complement components (Lewis and Ram, 2020; Skattum et al, 2011). Inclusion of participants with current or recent systemic infections could have confounded the evaluation of the safety profile of zilucoplan.
Is it considered to be included as missing information?	No
Rationale	"*Neisseria* infections, particularly meningococcal infections" has been selected as an important potential risk for zilucoplan. This risk is mentioned in the prescribing information for the approved C5 inhibitors eculizumab (Soliris®) and ravulizumab (Ultomiris®) and also established in genetic C5 deficiencies. No cases of *Neisseria* infections have been identified in the zilucoplan development program to date. Current evidence from patients with genetic complement deficiencies and from our understanding of the complement system shows that deficiencies of terminal complement components are almost exclusively associated with an increased risk of *Neisseria* infections (meningococcal and gonococcal infections). Zilucoplan does not inhibit early complement components, for which deficiencies are associated with an increased susceptibility for a number of other infections, eg, with other encapsulated bacteria (Lewis and Ram, 2020; Skattum et al, 2011). This is also supported by analyses from two eculizumab Phase 3 studies and their extensions in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder and acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (Levine et al, 2020) and data from the eculizumab PNH registry (Eculizumab EU-RMP 22 Jul 2019).

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Pregnancy	
Reason for exclusion	There are no adequate clinical data on the use of zilucoplan in pregnant women or lactating women. Female study participants who were pregnant, planning to become pregnant, or nursing were excluded. Female study participants of childbearing potential must have had a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug. Sexually active female study participants of childbearing potential and all male study participants (not surgically sterilized by vasectomy) agreed to use effective contraception during the study and during the safety follow-up period. Zilucoplan, when administered subcutaneously to pregnant cynomolgus monkeys in an enhanced pre-/post-natal development study, had no effect on pregnancy loss, embryo-fetal development, parturition and survival and postnatal development of the offspring. No maternal toxicity or effect on pregnancy outcome, the number of viable fetuses, or placental weights was noted. Fetal development was not affected, based on the absence of treatment-related effects including clinical signs, body weights, external examination for abnormalities, morphology, neurobehavioral assessments, grip strength, skeletal development, macroscopy and organ weights and immunophenotyping. Please refer to EU RMP Part II Module s7 for a summary of the ex-vivo closed-circuit human placental transfer model data.
Is it considered to be included as missing information?	Yes
Lactation	
Reason for exclusion	There are no adequate clinical data on the use of zilucoplan in lactating women. Potential transfer in breast milk has not been studied for zilucoplan. It is also not known whether zilucoplan is excreted in human milk.
Is it considered to be included as missing information?	Yes
Pediatrics (study participants <18 years of age)	
Reason for exclusion	Considering the proposed indication and GCP, it is a standard practice to initiate studies in the adult patient population. There are no adequate data on use of zilucoplan in children.
Is it considered to be included as missing information?	No

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	Pediatric studies are planned under a separate approved PIP (EMEA-002747-PIP01-20) and no efficacy and safety data in study participants aged from 2 to <18 years are available to support the initial submission. Use in pediatrics is not considered a part of the proposed indication population in the initial submission. As described in the PIP, it is not anticipated that pediatric patients with anti-AChR antibody positive gMG will respond differently to zilucoplan than adults, since there is no known difference in the pathophysiology between adult and juvenile gMG and development of the complement system is complete by 6 months of age. Thus, use in pediatrics is not considered as missing information as per EU GVP module V rev2.
Hypersensitivity to zilucoplan or any of its excipients	
Reason for exclusion	Hypersensitivity reactions have been reported in patients treated with zilucoplan. As a preventive measure, hypersensitivity is a standard exclusion criterion.
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity to zilucoplan or any of its excipients is a contraindication. In the zilucoplan development program, reported hypersensitivity reactions are usually local and no risk of systemic/anaphylactic reactions has been identified.

AChR=acetylcholine receptor; C5=complement component 5; GCP=Good Clinical Practice; gMG=generalized myasthenia gravis; GVP=Good Pharmacovigilance Practice; PIP=pediatric investigation plan; PNH=paroxysmal nocturnal hemoglobinuria; RMP=risk management plan

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

All clinical development programs are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. For rare disease programs, where the numbers of study participants available are limited, there is greater chance that the safety profile will be immature.

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 3–1 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Pregnant or breastfeeding women were not included in the clinical development program. As of the cutoff date, one pregnancy case and no cases of lactation were reported with maternal exposure to zilucoplan. This study participant became pregnant after discontinuation of zilucoplan (the date of last menstrual period was 1 day before the last zilucoplan administration) and delivered a healthy baby. She had been exposed to zilucoplan for more than a year prior to becoming pregnant.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with cardiovascular impairment • Immunocompromised patients	Study participants with cardiovascular impairment and immunocompromised participants were not specifically excluded from the zilucoplan studies in gMG.
Patients with relevant comorbidities: • Patients with a disease severity different from inclusion criteria in clinical trials	With regard to gMG severity, study participants with the following were not included in the zilucoplan studies in gMG: • MG-ADL Score of <6 at Screening and Baseline (Phase 3 study) • QMG Score of <12 at Screening and Baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours) (Phase 2 and 3 studies) • <4 of the QMG test items scored at ≥2 at Screening and Baseline (Phase 2 and 3 studies)

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment	Study participants with hepatic impairment were not specifically excluded from zilucoplan studies in gMG. UP0094 was a Phase 1, multicenter, open-label, clinical study to assess the single dose PK of zilucoplan and its metabolites (including RA103488 and RA102758) in study participants with moderate hepatic impairment and study participants with normal hepatic function. Sixteen study participants were enrolled into this study: 8 study participants with moderate hepatic impairment and 8 healthy study participants. Healthy study participants with normal hepatic function were matched individually to study participants with moderate hepatic impairment by age (±10 years), sex, weight (±10kg), and BMI (±15%). A single zilucoplan 0.3mg/kg dose was administered SC on Day 1. Zilucoplan systemic exposure (AUC) was 24% lower in moderate hepatic impairment study participants (Geo LSMeans ratio [90% CI]) (0.76 [0.65 to 0.88]) compared with study participants with normal liver function. The zilucoplan peak exposure was similar between study participants with moderate impaired liver function and study participants with normal liver function based on C_{max} Geo LSMeans ratio (90% CI) (0.95 [0.82 to 1.10]). Moderate hepatic impaired study participants had a 32% higher CL/F and ~36% Vz/F normalized to body weight (ie, 0.1107L/kg in moderate hepatic impaired study participants and 0.08164L/kg in study participants with normal liver function). As a consequence, the terminal half-life remained similar between the 2 arms indicating that despite moderate hepatic impairment, the metabolic function of the liver did not impact PK of zilucoplan. Pharmacodynamic analyses did not identify any meaningful differences in either C5 levels nor inhibition of complement activation by zilucoplan (sRBC lysis assay) between moderate hepatic impaired and normal study participants despite a 24% lower geometric mean in zilucoplan exposure (AUC). These results indicate that a zilucoplan dose adjustment in patients with moderately impaired liver function is not warranted. The safety and efficacy of zilucoplan in patients with severe hepatic impairment have not been established. No dose recommendation can be made.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with renal impairment	Study participants with renal impairment were not specifically excluded from zilucoplan studies in gMG. UP0114 was an open-label, single dose Phase 1 PK study of zilucoplan in study participants with severe renal impairment (as defined by a creatinine CL <30mL/min) and healthy controls who received a single dose of zilucoplan 0.3mg/kg SC. A total of 16 study participants were enrolled into this study: 8 study participants with severe renal impairment and 8 healthy control participants. The PK profiles of zilucoplan following SC administration were similar between healthy study participants and those with severe renal impairment. The mean C_{max} was 4830.3ng/mL in healthy study participants and 4468.7ng/mL in study participants with severe renal impairment. The mean $AUC_{0\text{-}inf}$ postdose was 821,508.2ng•h/mL in healthy study participants and 717,144.3ng•h/mL in those with severe renal impairment. The metabolite profiles were similar between healthy study participants and those with severe renal impairment. Based on these data, there is no significant impact of reduced creatinine clearance on the elimination of zilucoplan, and no dose adjustment is warranted for its use in patients with renal impairment.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Population with relevant different ethnic origin	Study participants with relevant different ethnic origin were not specifically excluded from zilucoplan studies in gMG. UP0113 was a randomized, double-blind, single and multiple dose Phase 1 pharmacokinetic study in healthy Japanese and Caucasian study participants who received a single dose of zilucoplan 0.1mg/kg SC (n=4 each, Japanese and Caucasian) or matching placebo (n=1 each, Japanese and Caucasian); a single dose of zilucoplan 0.3mg/kg SC (n=4 each, Japanese and Caucasian) or matching placebo (n=1 each, Japanese and Caucasian); and 14 daily doses of zilucoplan 0.3mg/kg SC (n=6 each, Japanese and Caucasian) or matching placebo (n=2 each, Japanese and Caucasian). The PK profiles of zilucoplan following SC administration were similar between healthy Japanese and Caucasian study participants in the multiple dose as well as the single dose cohorts. After 14 daily doses of zilucoplan 0.3mg/kg, mean C_{max} was 12,363ng/mL in healthy Caucasian study participants and 13,455ng/mL in healthy Japanese study participants. The mean $AUC_{0\text{-}last}$ after the last dose was 260,833ng·h/mL in Caucasian study participants and 274,667ng·h/mL in Japanese study participants. After a single dose of zilucoplan 0.3mg/kg (0.1mg/kg), mean C_{max} was 3587ng/mL (1706ng/ml) in the Caucasian group, and 3771ng/mL (1589ng/ml) in the Japanese group. After a single dose of zilucoplan 0.3mg/kg (0.1mg/kg), the mean $AUC_{0\text{-}inf}$ was 668,750ng·h/mL (448,750ng·h/mL) in Caucasian study participants and 815,500ng·h/mL (482,750ng·h/mL) in Japanese study participants. Dose proportionality and metabolite profile were similar between the Caucasian and Japanese study participants. Based on these data, no significant difference was detected between Caucasian and Japanese study participants with respect to zilucoplan's PK and PD profile. No specific adjustments to zilucoplan dosing are warranted for Japanese patients. Please refer to EU RMP Part II Module s3 for the exposure by ethnic origin.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Subpopulations with genetic polymorphisms were not excluded from zilucoplan studies. The binding site of zilucoplan on the C5 protein is distinct from that of the approved complement C5 inhibitory monoclonal antibody eculizumab. Nishimura and colleagues have described 11 patients in Japan (≈3.2% of the paroxysmal nocturnal hemoglobinuria population) who had a single missense C5 heterozygous mutation, c.2654G → A, which predicts the polymorphism p.Arg885His, that prevent the binding of eculizumab to C5 and who are thus resistant to treatment with the antibody (Nishimura et al, 2014). The Japanese study participants in MG0010 were tested for this specific missense C5 heterozygous mutation and none were found to have this mutation.

BMI=body mass index; C5=complement component 5; CI=confidence interval; CL/F=clearance corrected for bioavailability; Geo LS=geometric least squares; gMG=generalized myasthenia gravis; MG-ADL=myasthenia gravis activities of daily living; PD=pharmacodynamic; PK=pharmacokinetic; QMG=quantitative myasthenia gravis; RMP=risk management plan; SC=subcutaneous; sRBC=sheep red blood cell

PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

Zilucoplan is not currently marketed in any country, therefore this module is not applicable.

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The abuse and dependence potential of zilucoplan has not been evaluated in a dedicated clinical study, however, a detailed assessment of the abuse potential of zilucoplan has been conducted.

Based on the characteristics and target population of this drug, no evidence to suggest a potential for drug abuse or misuse is anticipated.

Zilucoplan potently and avidly binds to complement component 5 (C5), thereby preventing its cleavage into C5a and C5b. Although zilucoplan is the first peptide to bind to C5, an understanding of this pharmacological mechanism has been gained through experience with the C5 monoclonal antibodies, eculizumab and ravulizumab. The US Food and Drug Administration has concluded that eculizumab and ravulizumab, which are brain-penetrants and sequester C5 in the central nervous system, pose no risks for human abuse or dependence.

Although UCB has not conducted nonclinical or clinical studies to specifically assess the abuse and dependence potential of zilucoplan, the accumulated evidence demonstrates that inhibiting C5 carries no clinically significant risk for abuse or dependence in humans. Zilucoplan produced no behavioral or neurological effects in animals or subjective effects in humans to suggest that it has potential for abuse or dependence.

The evidence from chemical, nonclinical, and clinical sources consistently show that zilucoplan carries no risk for abuse or dependence in humans and that zilucoplan should not be a controlled drug.

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Table 1–1: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risk not considered important	Justification for non-inclusion in the list of safety concerns
Injection site reactions	Injection site reactions are well characterized. Most common terms were injection site bruising, pain, nodule, pruritis, hematoma and erythema. All events were nonserious, mild, or moderate in severity, and less than 3% of events led to treatment discontinuation. In pooled placebo-controlled gMG studies, injection site reactions were reported in 25.2% of patients treated with zilucoplan and in 15.5% treated with placebo. This risk has been anticipated given the subcutaneous administration of zilucoplan. It does not meet the criteria for important risk per the EU-GVP module V rev2 definition and is considered to have minimal benefit-risk and public health impact. Injections site reactions are proposed to be included as very common ADR in SmPC Section 4.8.
Upper respiratory tract infections	Most common terms were nasopharyngitis, upper respiratory tract infection, and sinusitis. More than 95% of cases were nonserious, mild or moderate in severity and did not lead to treatment discontinuation. In pooled placebo-controlled gMG studies, upper respiratory tract infections were reported in 13.0% of patients treated with zilucoplan and in 7.8% treated with placebo. This risk does not meet the criteria for important risk per the EU-GVP module V rev2 definition and is considered to have minimal benefit-risk and public health impact. Upper respiratory tract infections are proposed to be included as very common ADR in SmPC Section 4.8.
Amylase increased, Lipase increased	Elevations of lipase and/or amylase were observed. These were transient, and only one lead to treatment discontinuation. No causal relationship was identified between zilucoplan and pancreatitis. In pooled placebo-controlled gMG studies, TEAEs of amylase and lipase increased were reported in, respectively, 6.1% and 5.2% of patients treated with zilucoplan and in 2.9% (both amylase and lipase increased) treated with placebo. This risk does not meet the criteria for important risk per the EU-GVP module V rev2 definition and is considered to have minimal benefit-risk and public health impact. Amylase increased and lipase increased are proposed to be included as common ADR in SmPC Section 4.8.

Table 1–1: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risk not considered important	Justification for non-inclusion in the list of safety concerns
Blood eosinophils increased	Elevations of blood eosinophils were observed. These were transient, not leading to treatment discontinuation, and not associated with clinically relevant organ dysfunction. In pooled placebo-controlled gMG studies, the TEAE of eosinophilia was reported in 0.9% of patients treated with zilucoplan and 0% in patients treated with placebo. This risk does not meet the criteria for important risk per the EU-GVP module V rev2 definition and is considered to have minimal benefit-risk and public health impact. Blood eosinophils increased is proposed to be included as uncommon ADR in SmPC Section 4.8.
Diarrhoea	All events were non-serious, mild, or moderate in severity, and none led to treatment discontinuation. In pooled placebo-controlled gMG studies, TEAEs of diarrhoea were reported in 9.6% of patients treated with zilucoplan and in 2.9% treated with placebo. This risk does not meet the criteria for important risk per the EU-GVP module V Rev 2 definition and is considered to have minimal benefit-risk and public health impact. Diarrhoea is proposed to be included as common ADR in SmPC Section 4.8.
Morphea	Cases of morphea were observed after long-term zilucoplan treatment during the open label extension gMG study. The majority of the cases had a time to onset longer than one year after start of treatment, were mild or moderate in severity and did not lead to treatment discontinuation. This risk does not meet the criteria for important risk per the EU-GVP module V Rev 2 definition and is considered to have minimal benefit-risk and public health impact. Morphea is proposed to be included as common ADR in SmPC Section 4.8.

ADR=adverse drug reaction; gMG=generalized myasthenia gravis; GVP=Good Pharmacovigilance Practices; RMP=risk management plan; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event

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

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks: None	
Important potential risks	
***Neisseria* infections, particularly meningococcal infections**	
Risk-benefit impact	Zilucoplan mechanism of action is based on C5 inhibition. Deficiency of C5 and subsequent terminal complement components is associated with an increased incidence of infection with *Neisseria* species, in particular *Neisseria meningitidis*. Meningococcal infections are a medical emergency and can be life-threatening and potentially fatal when not recognized and treated timely. No *Neisseria* infections have been reported in the zilucoplan clinical development program to date, where patients were required to be vaccinated and/or receiving antibiotic prophylaxis. Risk of *Neisseria* infections, particularly meningococcal infections, has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Meningococcal infections are life-threatening (and potentially fatal) conditions with significant impact on patient's quality of life (especially if presenting with sequelae), hence, the implementation of additional risk minimization measures (see EU RMP Part V). A specific adverse reaction follow-up questionnaire for 'meningococcal infections' will be utilized in the postmarketing setting (see EU RMP Part VII Annex 4). Additional pharmacovigilance activities (see EU RMP Part III) will be implemented to monitor this risk. Information relating to *Neisseria* infections is described in SmPC Section 4.3 (Contraindications) and in SmPC Section 4.4 (Special warnings and Precautions for use). Further information is also provided in the Package Leaflet.
Missing information	
Use during pregnancy and lactation	

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk-benefit impact	In an enhanced pre-/post-natal development study, no adverse effects of zilucoplan have been observed on pregnant cynomolgus monkeys, on pregnancy or on fetal, and peri-and post-natal development of infant monkeys. In an ex-vivo closed-circuit human placental transfer model with experiments performed over a period of 6 hours, a low level of transplacental transfer of zilucoplan was observed at a transfer rate of 0.5-1.0%. At a steady state plasma concentration of 10µg/mL zilucoplan, which corresponds to a therapeutic dose of 0.3mg/kg, a transfer rate of 0.5% was observed. Based on results of this ex-vivo human placental transfer model, in-vivo transplacental transfer of zilucoplan cannot be excluded. Given the limitations of this model and the low transfer rate measured, there is still considerable uncertainty with respect to in-vivo placental transfer of zilucoplan and the clinical relevance of these data in human pregnancies is unknown. These results are not considered to have a significant impact on the benefit-risk balance of zilucoplan. It is not known whether zilucoplan is excreted in human breast milk or absorbed systematically after oral ingestion by the baby. There are no adequate clinical data on the use of zilucoplan in pregnant women or lactating women. A risk to the newborns/infants cannot be excluded (SmPC Section 4.6 Fertility, pregnancy and lactation). Further information is also provided in the Package Leaflet. Use during pregnancy and lactation is thus considered missing information.
Long-term safety	
Risk-benefit impact	Limited data are available on long-term use (> 1 year) of zilucoplan in adult patients with gMG. The available evidence in gMG and other indications (PNH and IMNM) is not suggestive for a different safety profile compared to short term use. Further data are being collected in the ongoing clinical development program. Long-term safety data is thus considered a missing information.

C5=complement component 5; gMG=generalized myasthenia gravis; IMNM=immune-mediated necrotizing myopathy; PNH=paroxysmal nocturnal hemoglobinuria; RMP=risk management plan; SmPC=summary of product characteristics

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

This section is not applicable since this is the initial RMP for zilucoplan.

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

3.1 Presentation of important identified risks and important potential risks

3.1.1 Important identified risks

None.

3.1.2 Important potential risks

Important potential risks with zilucoplan treatment are characterized in Table 3–1.

Table 3–1: Important potential risk: *Neisseria* infections, particularly meningococcal infections

Potential mechanism(s)	Zilucoplan mechanism of action is based on C5 inhibition. Deficiency of terminal complement components is associated with an increased incidence of infection with *Neisseria* species, in particular *Neisseria meningitidis*, as *Neisseria* bacteria are primarily cleared by the terminal complement components (Lewis and Ram, 2020; Skattum et al, 2011). Current evidence from patients with genetic complement deficiencies and our understanding of the complement system shows that deficiencies of terminal complement components are almost exclusively associated with an increased risk of *Neisseria* infections (meningococcal and gonococcal infections). Zilucoplan does not inhibit early complement components, for which deficiencies are associated with an increased susceptibility for a number of other infections, eg, with other encapsulated bacteria (Lewis and Ram, 2020; Skattum et al, 2011). This is also supported by analyses from 2 eculizumab Phase 3 studies and their extensions in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder and acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (Levine et al, 2020) and data from the eculizumab PNH registry (Eculizumab EU RMP 22 Jul 2019).
Evidence source(s) and strength of evidence	This important potential risk is based on zilucoplan mechanism of action, on experience with approved drugs with a similar mechanism of action eculizumab (Soliris®) and ravulizumab (Ultomiris®), evidence from patients with genetic complement deficiencies, and our understanding of the complement system.
Characterization of the risk	Frequency To date, no cases of *Neisseria* infections have been reported in zilucoplan-treated patients. Severity Meningococcal infections are a medical emergency and can be life-threatening and potentially fatal when not recognized and treated timely. Gonococcal infections can be usually treated ambulatory, except for disseminated forms (1-3%) which require hospitalization and intravenous antibiotics. Reversibility and long-term outcome

Table 3–1: Important potential risk: *Neisseria* infections, particularly meningococcal infections

	Acute meningococcal infection must be timely treated with antibiotics and patients usually recover after such treatment, although long-term sequelae have been reported in 10–20% of patients (Olbrich et al, 2018). Gonococcal infections can be usually successfully treated with antibiotics but untreated gonorrhea can lead to major complications such as infertility. Impact on quality of life Since meningococcal infections are serious and life-threatening diseases, requiring hospitalization and treatment, the impact on a patients' quality of life is significant. Moreover, neurological, physical and psychological sequelae can also have long-term impact on a patient's quality of life (Olbrich et al, 2018). For gonococcal infections, the impact on quality of life can be considered minor, except for disseminated infections, pregnancy loss, and complications after untreated gonorrhea. Of note, apart from meningococcal and gonococcal infections, also a number of postmarketing reports of serious infections caused by typically commensal *Neisseria* bacteria have been identified in patients treated with eculizumab (Crew et al, 2019).
Risk factors and risk groups	Main risk factors for meningococcal infections include: - Congenital immunodeficiency (Taha et al, 2021) - History of hemopoietic stem cell transplantation (Taha et al, 2021) - Acquired immunodeficiency disorders (Taha et al, 2021) - Human immunodeficiency virus (Taha et al, 2021) - Asplenia or hyposplenia (Taha et al, 2021) - Chronic liver disease (Taha et al, 2021) - Acute upper and lower respiratory tract infections (Taha et al, 2021; Spyromitrou-Xioufi et al, 2020) - History of severe chronic disorders: autoimmune disease, hemophilia (Taha et al, 2021) - Low income and living in a relatively socially deprived community were both associated with an increased risk of hospitalization for invasive meningococcal disease (Taha et al, 2021) - Debilitating disease (Taha et al, 2021) - Age: incident meningococcal infections cases was higher among aged 0-2 and 15-24 years old (Taha et al, 2021) - Household crowding (Spyromitrou-Xioufi et al, 2020) - Smoking exposure (Spyromitrou-Xioufi et al, 2020) - Close relationships (Spyromitrou-Xioufi et al, 2020) - Sexual relationships between men (Folaranmi et al, 2017) - Genetic deficiency or therapeutic inhibition of terminal complement (Hodeib et al, 2020) - Lack of vaccine coverage in the developing world: meningococcal

Table 3–1: Important potential risk: *Neisseria* infections, particularly meningococcal infections

	vaccination plays a major role in the control of the disease (Shaker et al, 2018) Main risk factors for gonococcal infections include: - Age (Gale et al, 2017; Mayor et al, 2012; Bjekic et al, 1997) - Gender (Gale et al, 2017) - Low education level (Bjekic et al, 1997) - Low socioeconomic status (Bjekic et al, 1997) - Multiple sexual partners (Dela et al, 2019; Mayor et al, 2012) - Alcohol use in males (Dela et al, 2019) - Frequency of condom use in females (Dela et al, 2019) - Black race (Mayor et al, 2012) - History of previous gonococcal infection or other sexually transmitted infections (Mayor et al, 2012) - Inconsistent condom use (Mayor et al, 2012) - Men who have sex with men (Mayor et al, 2012) - Prostitution (Mayor et al, 2012) - Substance abuse (Mayor et al, 2012) No data were identified as additional risk factors for meningococcal or gonococcal infections related to gMG.
Preventability	Use of zilucoplan is contraindicated in patients who are not currently vaccinated against *Neisseria meningitidis* and in patients with unresolved *Neisseria meningitidis* infection (SmPC Section 4.3 Contraindications). Increased awareness of HCP and patient about the risk of meningococcal infections and the suggestive signs and symptoms will be implemented in minimizing the risk. As a precautionary measure, all patients must be vaccinated against meningococcal infection, at least 2 weeks prior to the start of treatment with zilucoplan. Patients who start treatment with zilucoplan less than 2 weeks after vaccination against meningococcal infection should receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose. Vaccines against serogroups A, C, Y, W, and, where available, serogroup B, are recommended for preventing the commonly pathogenic meningococcal serogroups. Vaccination and prophylactic antibacterial treatment should occur according to most current relevant vaccination guidelines. It is recognized that meningococcal vaccination may not prevent all cases of meningococcal infections. Measures such as meningococcal vaccination and antibiotic prophylaxis are discussed in SmPC Section 4.4 (Special warnings and precautions for use). Refer to EU RMP Part V for a detailed description of additional risk minimization measures for zilucoplan, designed to prevent and/or minimize the risk of meningococcal infections.

Table 3–1: Important potential risk: *Neisseria* infections, particularly meningococcal infections

	With respect to gonococcal infections, patients should be counseled about the importance of gonorrhea prevention and treatment.
Impact on risk-benefit balance of the product	Meningococcal infections are a medical emergency and can be life-threatening and potentially fatal when not recognized and treated timely. They can have significant impact on a patient's quality of life (especially if they lead to sequelae), hence the implementation of additional risk minimizations measures (see EU RMP Part V). No *Neisseria* infections have been reported in the zilucoplan clinical development program to date, where patients were required to be vaccinated and/or receiving antibiotic prophylaxis. A specific adverse reaction follow-up questionnaire for 'meningococcal infections' will be utilized in the postmarketing setting (see EU RMP Part VII Annex 4). Additional pharmacovigilance activities (see EU RMP Part III) will be implemented to monitor this risk. Information relating to *Neisseria* infections is described in SmPC Section 4.3 (Contraindications) and in SmPC Section 4.4 (Special warnings and precautions for use). Further information is also provided in the Package Leaflet.
Public health impact	The absolute risk of *Neisseria* infections in patients with adequate meningococcal vaccination and/or antibiotic prophylaxis is considered low. Public health impact of meningococcal and gonococcal infections is mainly in the need for measures to avoid spreading the infection to additional persons.

C5=complement component 5; gMG=generalized myasthenia gravis; HCP=healthcare professional; PNH= paroxysmal nocturnal hemoglobinuria; RMP=risk management plan; SmPC=summary of product characteristics

3.2 Presentation of the missing information

3.2.1 Use during pregnancy and lactation

Evidence source:

In an enhanced pre-/post-natal development study, no adverse effects of zilucoplan have been observed on pregnant cynomolgus monkeys, on pregnancy or on fetal, and peri-and post-natal development of infant monkeys.

In an ex-vivo closed-circuit human placental transfer model with experiments performed over a period of 6 hours, a low level of transplacental transfer of zilucoplan was observed at a transfer rate of 0.5-1.0%. At a steady state plasma concentration of 10µg/mL zilucoplan, which corresponds to a therapeutic dose of 0.3mg/kg, a transfer rate of 0.5% was observed. Based on results of this ex-vivo human placental transfer model, in-vivo transplacental transfer of zilucoplan cannot be excluded. Given the limitations of this model and the low transfer rate measured, there is still considerable uncertainty with respect to in-vivo placental transfer of Zilucoplan and the clinical relevance of these data in human pregnancies is unknown. These results are not considered to have a significant impact on the benefit-risk balance of zilucoplan.

It is not known whether zilucoplan is excreted in human breast milk.

There are no adequate clinical data on the use of zilucoplan in pregnant women or lactating women. As of the cutoff date, one pregnancy case and no cases of lactation were reported with maternal exposure to zilucoplan. This study participant became pregnant after discontinuation of zilucoplan (the date of last menstrual period was 1 day before the last zilucoplan administration) and delivered a healthy baby. She had been exposed to zilucoplan for more than a year prior to becoming pregnant.

Population in need of further characterization:

The safety and efficacy of zilucoplan in pregnant or breastfeeding women has not been established.

3.2.2 Long-term safety

Evidence source:

Limited data are available on long-term use (> 1 year) of zilucoplan in adult patients with gMG. The available evidence in gMG and other indications (paroxysmal nocturnal hemoglobinuria [PNH] and IMNM) is not suggestive for a different safety profile compared to short term use.

Population in need of further characterization:

Patients under long-term treatment with zilucoplan.

PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	*Neisseria* infections, particularly meningococcal infections
Missing information	Use during pregnancy and lactation Long-term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- A specific adverse reaction follow-up questionnaire form for 'meningococcal infections' will be utilized in the postmarketing setting.

  This structured follow-up form is designed to optimize documentation of case reports of meningococcal infection by means of collecting detailed information in a structured and standardized manner.

  The proposed questionnaire aims to collect information on the patient, exposure to zilucoplan and other complement inhibitors, clinical presentation and diagnostic investigations, vaccination and antibiotic prophylaxis, relevant medical history and risk factors of meningococcal infections, treatment, and outcome of the event.

  The proposed follow-up questionnaire form is provided in EU RMP Part VII Annex 4.

- Other forms of routine pharmacovigilance activities: None

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

2.1 Zilucoplan observational secondary data PASS (MG0026)

Study short name and title:

A multi-national cohort study to assess the implementation of the RMM to prevent meningococcal infection in gMG patients initiated with zilucoplan, and the risk of serious infections.

Rationale and study objectives:
The main aims of this study are to assess the implementation of RMM to prevent meningococcal infections and to describe serious meningococcal infections in gMG patients exposed and unexposed to zilucoplan (exposed to other gMG treatments).
In addition, serious infections will be described in gMG patients exposed to zilucoplan and compared to patients unexposed to zilucoplan (exposed to other gMG treatments); gMG treatment usage in real-world settings and the safety profile of zilucoplan used during pregnancy will also be described.

Objectives apply to all countries in the study (France, Germany, and US), except for objective 1 where only European data sources will be used.

The primary objective of this study will be:

- To assess the implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice in France and Germany by examining the percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and if appropriate prophylactic antibiotic treatment is received when the zilucoplan treatment

is initiated less than 2 weeks after the first vaccination dose against meningococcal infection.

The secondary objectives will be:

- To describe serious meningococcal infections in patients with gMG who are new users of zilucoplan or users of other comparable gMG treatments (efgartigimod, eculizumab, ravulizumab, rozanolixizumab, rituximab, immunoglobulins, and PLEX).
- To characterize zilucoplan or comparable gMG treatment users and describe their gMG treatment usage in real-world settings.
- To estimate the risk of serious infections among gMG patients, comparing new users of zilucoplan with users of other comparable gMG treatments.
- To describe pregnancy and birth outcomes in women with gMG exposed during pregnancy to zilucoplan or other gMG comparable treatments, and infant outcomes up to the first year of life.

Study design:

Non-interventional multi-national comparative cohort using a prevalent new user design.

Study population:

Adult gMG patients identified in European and US databases who initiate zilucoplan or receive other gMG treatment(s). The other gMG treatments considered (as comparator treatments) will be efgartigimod, eculizumab, ravulizumab, rozanolixizumab, rituximab, immunoglobulins, and PLEX.

Milestones:

Protocol submission: will be submitted for Pharmacovigilance Risk Assessment Committee (PRAC) review before initiation of the study (6 months after marketing authorization in Europe).

Interim report submission: 01 Jun 2026

Final report submission: 01 Dec 2028

For further details please see EU RMP Part VII Annex 3 for the PASS detailed synopsis.

2.2 MG0011 (RAISE-XT)

Study short name and title:

A Phase 3, multicenter, open-label extension study of zilucoplan in study participants with gMG.

Rationale and study objectives:

The primary objective of MG0011 is to evaluate the long-term safety and tolerability of zilucoplan and the secondary objective is to assess long-term efficacy of zilucoplan in study participants with gMG.

Study design:

Open-label, uncontrolled study. Study participants will receive 0.3mg/kg zilucoplan administered SC at the Day E1 visit. All study participants will self-inject daily SC doses of study drug for the

subsequent doses. Single use pre-filled syringes in injection devices will be provided for use during the study.

Study population:

Adults study participants with gMG who previously participated in the parent zilucoplan studies (MG0009 or MG0010).

Milestones:

This study is ongoing since 23 Dec 2019 (First Patient First Visit).

Final report submission: 30 Nov 2026

For further details, please see EU RMP Part VII Annex 3 for the study protocol.

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table 3–1.

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				
Observational secondary data PASS (MG0026) Planned	To assess the implementation of the RMM, to evaluate any potential increase in the risk of serious infections for zilucoplan exposed gMG patients compared to gMG patients not exposed to zilucoplan(exposed to other gMG treatments) and to describe other safety outcomes of interest.	Important potential risk: *Neisseria* infections, particularly meningococcal infections Missing information: Use of zilucoplan during pregnancy and long-term safety	Protocol submission	Will be submitted for PRAC review before initiation of the study (6 months after marketing authorization in Europe).
			Interim report submission	01 Jun 2026
			Final report submission	01 Dec 2028

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
MG0011 (RAISE-XT) - A Phase 3, multicenter, open-label extension study of zilucoplan in study participants with gMG Ongoing	To assess the long-term safety, tolerability, and efficacy of zilucoplan in study participants with gMG.	Missing information: long-term safety	Final report submission	30 Nov 2026

gMG=generalized myasthenia gravis; PASS=postauthorization safety study; PRAC=Pharmacovigilance Risk Assessment Committee; RMM=risk minimization measure

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for zilucoplan.

RMP PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

1 ROUTINE RISK MINIMIZATION MEASURES

Description of RMMs by safety concern is presented in Table 1–1.

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
None	
Important potential risks	
Neisseria infections, particularly meningococcal infections	**Routine risk communication:** Use of zilucoplan is contraindicated in patients who are not currently vaccinated against *Neisseria meningitidis* and in patients with unresolved *Neisseria meningitidis* infection (SmPC Section 4.3 Contraindications). Risk of *Neisseria* infections is discussed in SmPC Section 4.4 (Special warnings and precautions for use) and in PL Section 2 (What you need to know before you use Zilbrysq). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Measures such as meningococcal vaccination and antibiotic prophylaxis are discussed in SmPC Section 4.4 (Special warnings and precautions for use), PL Section 2 (What you need to know before you use Zilbrysq), and in PL Section 3 (How to use Zilbrysq). Information on signs and symptoms of meningococcal infections is discussed in SmPC Section 4.4 (Special warnings and precautions for use) and in PL Section 2 (What you need to know before you use Zilbrysq). **Other routine risk minimization measure beyond the Product Information:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration).
Missing information	

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Use during pregnancy and lactation	**Routine risk communication:** SmPC Section 4.6 (Fertility, pregnancy, and lactation) PL Section 2 (What you need to know before you use Zilbrysq) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 (Fertility, pregnancy, and lactation) PL Section 2 (What you need to know before you use Zilbrysq) **Other routine risk minimization measure beyond the Product Information:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration).
Long-term safety	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration).

PL=package leaflet; SmPC=summary of product characteristics

2 ADDITIONAL RISK MINIMIZATION MEASURES

Additional RMMs include a CAP and educational materials for HCPs involved in MG management (prescribing physicians), patients, and caregivers, to reinforce the key safety information in the SmPC and the Package Leaflet (PL) with the aim to further minimize the risk of meningococcal infection.

2.1 Controlled access program

Objectives:

The aim of this program is to ensure that only patients who have been vaccinated against *Neisseria meningitidis* have access to zilucoplan. Verification of vaccination is achieved via written confirmation from the prescriber.

Rationale for the additional risk minimization activity:

This program is designed to control access to zilucoplan beyond the level of control ensured by routine RMMs, which consist mainly of a contraindication for patients who are not currently

vaccinated against *Neisseria meningitidis*. This additional level of control is expected to further minimize the risk of meningococcal infection.

Target audience and planned distribution path:

Prescribing physician and pharmacists dispensing the drug

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

The implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice will be assessed in a PASS (see EU-RMP Part VII Annex 3). The percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and of patients with appropriate prophylactic antibiotic treatment, when zilucoplan treatment is initiated less than 2 weeks after the first vaccination dose, will be provided.

Safety outcomes indicators will involve analysis of incidence of meningococcal infections. Both behavioral process indicators and safety outcome indicators will be evaluated through the PASS study, in addition to routine pharmacovigilance activities.

2.2 Educational materials

2.2.1 Guide for HCPs

Objectives:

- Enhance awareness of HCPs involved in MG management (prescribing physicians) of the important potential risk of meningococcal infection.
- Remind HCPs of meningococcal vaccination and antibiotic prophylaxis requirements.
- Inform HCPs on the CAP to ensure that only patients who have been vaccinated against meningococcal infection have access to zilucoplan.
- Promote monitoring for signs and symptoms of meningococcal infection.
- Provide recommendations for measures to take in case of suspected meningococcal infection.
- Remind prescribers to counsel patients on the risk of meningococcal infection and provide them the educational materials.

Rationale for the additional risk minimization activity:

This educational tool is proposed to reinforce the importance of prevention and early diagnosis of meningococcal infection.

Target audience and planned distribution path:

The primary audience is HCPs involved in MG management (prescribing physicians). In addition to paper versions of the educational materials, they will also be made available through a dedicated website targeted to HCPs. Healthcare professionals will be able to review and download the educational materials and order additional paper versions of the materials. The distribution path will be agreed at national level.

More details of educational material are provided in EU RMP Part VII Annex 6.

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

The implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice will be assessed in a PASS (see EU-RMP Part VII Annex 3). The percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and of patients with appropriate prophylactic antibiotic treatment, when zilucoplan treatment is initiated less than 2 weeks after the first vaccination dose, will be provided.

Safety outcomes indicators will involve analysis of incidence of meningococcal infections. Both behavioral process indicators and safety outcome indicators will be evaluated through the PASS study, in addition to routine pharmacovigilance activities.

2.2.2 Patient/Carer Guide

Objectives:

- To educate patients/carers about the detection and proper management of meningococcal infection.
- Remind patients/carers on the importance of receiving vaccination and prophylactic antibiotics, as applicable.
- Inform patients/carers on the CAP to ensure that only patients who have been vaccinated against meningococcal infection have access to zilucoplan.
- To instruct patients/carers and HCPs about the signs and symptoms of possible meningococcal infection and when to seek medical attention.

Rationale for the additional risk minimization activity:

To inform patients/carers about the risk of meningococcal infection that may lead to a fatal outcome. Patients must be trained to seek immediate medical care as soon as they experience any signs and symptoms of meningococcal infection and to carry their Patient Alert Card with them at all times and present it to HCPs.

Target audience and planned distribution path:

MG patients (and/or their caregivers)

In addition to paper versions of the educational materials, HCPs involved in treatment of the patient at any time will be able to download a printed version of the Patient Guide through a dedicated website targeted to HCPs. The distribution path will be agreed at national level.

More details of educational material are provided in EU RMP Part VII Annex 6.

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

The implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice will be assessed in a PASS (see EU-RMP Part VII Annex 3). The percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and of patients with appropriate prophylactic antibiotic treatment, when zilucoplan treatment is initiated less than 2 weeks after the first vaccination dose, will be provided.

Safety outcomes indicators will involve analysis of incidence of meningococcal infections. Both behavioral process indicators and safety outcome indicators will be evaluated through the PASS study, in addition to routine pharmacovigilance activities.

2.2.3 Patient Alert Card

Objectives:

- Enhance awareness of patients/caregivers of the important potential risk of meningococcal infection and its prevention.
- Promote monitoring for early and emergency signs of meningococcal infection and seeking medical attention (patients) and adequate investigations (HCPs) should these develop.

Rationale for the additional risk minimization activity:

This educational tool is proposed to reinforce the importance of prevention and early diagnosis of meningococcal infection.

Target audience and planned distribution path:

Patients (and/or their caregivers) who have been prescribed zilucoplan are intended to keep this card with them at all times, so the information reaches the relevant HCP as appropriate.

In addition to paper versions of the educational materials, HCPs involved in treatment of the patient at any time will be able to download a printed version of the Patient Alert Card through a dedicated website targeted to HCPs. The distribution path will be agreed at national level.

More details of educational material are provided in EU RMP Part VII Annex 6.

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

The implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice will be assessed in a PASS (see EU-RMP Part VII Annex 3). The percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and of patients with appropriate prophylactic antibiotic treatment, when zilucoplan treatment is initiated less than 2 weeks after the first vaccination dose, will be provided.

Safety outcomes indicators will involve analysis of incidence of meningococcal infections. Both behavioral process indicators and safety outcome indicators will be evaluated through the PASS study, in addition to routine pharmacovigilance activities.

2.3 Vaccination reminders for prescribers

Objectives

To remind prescribers to verify and ensure that their patient's vaccination against meningococcal infection is still current according to relevant vaccination guidelines.

Rationale for the additional risk minimization activity:

To highlight the importance of an effective vaccination against meningococcal infection to minimize this important potential risk.

Target audience and planned distribution path:

Prescribing physicians.

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

The Marketing Authorization Holder (MAH) ensures the reminder (letter) is sent annually to prescribing physicians.

The implementation of the vaccination RMM to prevent meningococcal infections in gMG patients who initiate zilucoplan in routine clinical practice will be assessed in a PASS (see EU-RMP Part VII Annex 3). The percentage of new users of zilucoplan with a vaccination against meningococcal infection in the prior 3 years and up to 14 days before zilucoplan initiation and of patients with appropriate prophylactic antibiotic treatment, when zilucoplan treatment is initiated less than 2 weeks after the first vaccination dose, will be provided.

Safety outcomes indicators will involve analysis of incidence of meningococcal infections. Both behavioral process indicators and safety outcome indicators will be evaluated through the PASS study, in addition to routine pharmacovigilance activities.

3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 3–1 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures (RMMs)	Pharmacovigilance (PhV) activities
Important identified risks		
None		
Important potential risks		

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures (RMMs)	Pharmacovigilance (PhV) activities
Neisseria infections, particularly meningococcal infections	**Routine RMMs:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindications). Measures such as meningococcal vaccination and antibiotic prophylaxis are discussed in SmPC Section 4.4 (Special warnings and precautions for use), PL Section 2 (What you need to know before you use Zilbrysq), and PL Section 3 (How to use Zilbrysq). Risk of *Neisseria* infections and information on signs and symptoms of meningococcal infections are discussed under SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (What you need to know before you use Zilbrysq). **Additional RMMs for meningococcal infections:** Controlled access program Educational materials - Guide for HCPs - Patient Alert Card - Patient/Carer Guide Vaccination reminders for prescribers	**Routine PhV activities beyond adverse reactions reporting and signal detection:** A specific adverse reaction follow-up questionnaire for 'meningococcal infections' will be utilized in the postmarketing setting. **Additional PhV activities:** Zilucoplan observational secondary data postauthorization safety study (MG0026).
Missing information		

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures (RMMs)	Pharmacovigilance (PhV) activities
Use during pregnancy and lactation	**Routine RMMs:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.6 (Fertility, Pregnancy, and Lactation). PL Section 2 (What you need to know before you use Zilbrysq) **Additional RMMs:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** Zilucoplan observational secondary data postauthorization safety study (MG0026).
Long-term safety	**Routine RMMs:** Zilucoplan is intended for use under the guidance and supervision by specialist healthcare professionals experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). **Additional RMMs:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** Zilucoplan observational secondary data postauthorization safety study (MG0026). Zilucoplan open-label extension study (MG0011/RAISE-XT)

HCP=healthcare professional; PhV=pharmacovigilance; PL=package leaflet; RMM=risk minimization measure; SmPC=summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zilbrysq (zilucoplan)

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

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

This summary of the RMP for Zilbrysq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

1 THE MEDICINE AND WHAT IT IS USED FOR

Zilbrysq is authorised as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. It contains zilucoplan as the active substance (approximately 0.3mg/kg) and it is given by subcutaneous injection once daily.

Further information about the evaluation of Zilbrysq’s benefits can be found in Zilbrysq’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: <link to the EPAR summary landing page>.

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

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

Measures to minimize 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 minimize its risks.

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

In the case of Zilbrysq, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report 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 Zilbrysq is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of Zilbrysq are risks that need special risk management activities to further investigate or minimize 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 Zilbrysq. 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 2–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	*Neisseria* infections, particularly meningococcal infections
Missing information	Use during pregnancy and lactation Long-term safety

2.2 Summary of important risks

Table 2–2: Summary of important risks

Important potential risk: *Neisseria* infections, particularly meningococcal infections	
Evidence for linking the risk to the medicine	This important potential risk is based on zilucoplan mechanism of action, on experience with approved drugs with a similar mechanism of action eculizumab (Soliris®) and ravulizumab (Ultomiris®), evidence from patients with genetic complement deficiencies, and our understanding of the complement system.
Risk factors and risk groups	Main risk factors for meningococcal infections include: - Congenital immunodeficiency (Taha et al, 2021) - History of hemopoietic stem cell transplantation (Taha et al, 2021) - Acquired immunodeficiency disorders (Taha et al, 2021) - Human immunodeficiency virus (Taha et al, 2021) - Asplenia or hyposplenia (Taha et al, 2021) - Chronic liver disease (Taha et al, 2021) - Acute upper and lower respiratory tract infections (Taha et al, 2021; Spyromitrou-Xioufi et al, 2020) - History of severe chronic disorders: autoimmune disease, hemophilia

Table 2–2: Summary of important risks

	(Taha et al, 2021) - Low income and living in a relatively socially deprived community were both associated with an increased risk of hospitalization for invasive meningococcal disease (Taha et al, 2021) - Debilitating disease (Taha et al, 2021) - Age: incident meningococcal infections cases was higher among aged 0-2 and 15-24 years old (Taha et al, 2021) - Household crowding (Spyromitrou-Xioufi et al, 2020) - Smoking exposure (Spyromitrou-Xioufi et al, 2020) - Close relationships (Spyromitrou-Xioufi et al, 2020) - Sexual relationships between men (Folaranmi et al, 2017) - Genetic deficiency or therapeutic inhibition of terminal complement (Hodeib et al, 2020) - Lack of vaccine coverage in the developing world: meningococcal vaccination plays a major role in the control of the disease (Shaker et al, 2018) Main risk factors for gonococcal infections include: - Age (Gale et al, 2017; Mayor et al, 2012; Bjekic et al, 1997) - Gender (Gale et al, 2017) - Low education level (Bjekic et al, 1997) - Low socioeconomic status (Bjekic et al, 1997) - Multiple sexual partners (Dela et al, 2019; Mayor et al, 2012) - Alcohol use in males (Dela et al, 2019) - Frequency of condom use in females (Dela et al, 2019) - Black race (Mayor et al, 2012) - History of previous gonococcal infection or other sexually transmitted infections (Mayor et al, 2012) - Inconsistent condom use (Mayor et al, 2012) - Men who have sex with men (Mayor et al, 2012) - Prostitution (Mayor et al, 2012) - Substance abuse (Mayor et al, 2012) No data were identified as additional risk factors for meningococcal or gonococcal infections related to gMG.
Risk minimization measures	Routine risk minimization measures: - SmPC Section 4.3 (Contraindications) and SmPC Section 4.4 (Special warnings and precautions for use) - PL Section 2 (What you need to know before you use ZILBRYSQ) Measures such as meningococcal vaccination and antibiotic prophylaxis are discussed in SmPC Section 4.4 (Special warnings and precautions for use), PL Section 2 (What you need to know before you use ZILBRYSQ), and PL Section 3 (How to use ZILBRYSQ).

Table 2–2: Summary of important risks

	Signs and symptoms of meningococcal infections are listed in SmPC Section 4.4 (Special warnings and precautions for use) and PL Section 2 (What you need to know before you use ZILBRYSQ). Use under guidance and supervision by specialist HCPs experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). Additional risk minimization measures for meningococcal infections: Controlled access program Educational materials - Guide for HCPs - Patient Alert Card - Patient/Carer Guide Vaccination reminders for prescribers
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Zilucoplan observational secondary data postauthorization safety study (MG0026). See Section 2.3 of this summary for an overview of the postauthorization plan.
Missing information: Use during pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: - SmPC Section 4.6 (Fertility, pregnancy and lactation) - PL Section 2 (What you need to know before you use ZILBRYSQ) Use under guidance and supervision by specialist HCPs experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Zilucoplan observational secondary data postauthorization safety study (MG0026). See Section 2.3 of this summary for an overview of the postauthorization plan.
Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: Use under guidance and supervision by specialist HCPs experienced in the management of patients with neuromuscular disorders (SmPC Section 4.2 Posology and method of administration). Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Zilucoplan observational secondary data postauthorization safety study (MG0026).

Table 2–2: Summary of important risks

	Open-label extension study (MG0011/RAISE-XT) See Section 2.3 of this summary for an overview of the postauthorization plan.

gMG=generalized myasthenia gravis; HCP=healthcare professional; PL=package leaflet; SmPC=summary of product characteristics

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of Zilbrysq.

2.3.2 Other studies in postauthorisation development plan

Additional pharmacovigilance activities include the following studies:

2.3.2.1 Zilucoplan observational secondary data postauthorization safety study (MG0026)

Purpose of the study: The overall aim of this postauthorization safety study will be to assess the effectiveness of the risk minimization measures, as well as the incidence of important outcomes of interest in routine practice for patients with gMG receiving zilucoplan treatment.

2.3.2.2 Open-label extension study (MG0011/RAISE-XT)

Purpose of the study: the objective of the study is to evaluate the long-term safety, tolerability, and efficacy of zilucoplan in study participants with gMG.

RMP PART VII: ANNEXES

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

A specific adverse reaction follow-up questionnaire form will be utilized in the postmarketing setting for ‘meningococcal infections’. The proposed follow-up questionnaire form is included below.

Identifier: UCB Global DS database #: _____

UCB LAM ID #: _____

For completion by UCB Patient Safety

Section A. Patient Information

Date of birth _____ (DD-MON-YYYY) OR **Age at time of the event** (if known): _____ years

OR Age category

[ ] Child (< 12 years) [ ] Adolescent (12-17 years) [ ] Adult (18-65 years) [ ] Elderly (> 65 years)

Sex assigned at birth: [ ] Female [ ] Male [ ] Intersex/Undifferentiated OR [ ] Prefer not to disclose

Country of residence:_____

Race/ethnicity (specify):_____

Weight_____ (Specify lbs. or kg); **Height**_____ (specify feet (ft.) and inches (in.)/ or meters (m))

Section B. Zilucoplan Drug Exposure Information

Please indicate dates in DD-MON-YYYY format

Disease indication for zilucoplan (specify): _____

Was zilucoplan administered prior to the occurrence of the adverse event ? [ ] Yes [ ] No [ ] Unknown

Zilucoplan dosing details

Total daily dose of zilucoplan: (check as applicable): [ ] 16.6 mg [ ] 23.0 mg [ ] 32.4 mg

other (specify):_____

Administration schedule: [ ] daily other (specify):_____

First dose of zilucoplan administered on _____

Last dose of zilucoplan administered PRIOR to adverse event onset was on _____

Action taken with zilucoplan

[ ] Drug administration continued
[ ] Drug administration interrupted; Interruption start date:_____
Number of doses missed _____ Dosing resumed on _____(date)
[ ] Drug administration was discontinued on _____ (date) and the final dose was administered on _____ (date)
[ ] Other action taken (such as dose reduction): _____
[ ] Not applicable
[ ] Unknown

Lot / Batch # _____ (check [ ] if not known)

Section C. Other Complement Inhibitor Information

Please indicate dates in DD-MON-YYYY format

Has the patient taken eculizumab (Soliris) up to 3 months prior to meningococcal infection onset?

[ ] Yes [ ] No [ ] Unknown

Has the patient taken ravulizumab (Ultomiris) up to 8 months prior to meningococcal infection onset?

[ ] Yes [ ] No [ ] Unknown

→ **Complete the rest of this section if <u>Yes</u> is indicated for either question above**

Indication for eculizumab (Soliris) treatment _____

Date eculizumab treatment started: _____

Date eculizumab treatment ended: _____

Indication for ravulizumab(Ultomiri) treatment _____

Date ravulizumab treatment started:_____

Date ravulizumab treatment ended: _____

Other complement inhibitor (specify):_____

Date treatment started:_____

Date treatment ended:_____

Section D. Description of event signs and/or symptoms

Onset Date of first symptom(s): → _____(DD-MON-YYYY format)

1. **Please tick all signs and/or symptoms** [✓]		
	Headache	[ ]
	Fever (*subjective or measured, and if measured provide exact body temperature*)	[ ] Temperature°C/°F: _____
	Hypothermia	[ ]
	Chills	[ ]
	Convulsions	[ ]
	Malaise (feeling unwell)	[ ]
	Myalgia (muscle aches and pains)	[ ]
	Neck stiffness	[ ]
	Back stiffness	[ ]
	Rash Petechiae present? Purpura present?	[ ] [ ] [ ]
	Nausea	[ ]
	Vomiting	[ ]
	Increased sensitivity to light (photophobia)	[ ]

	Altered mental status (e.g., confusion or drowsiness) If yes, please specify:	[ ]
	Other signs or symptoms(s) If yes, please specify :	[ ]

2. Meningococcal infection details (i.e., previous history, risk factors for current infection)

Previous history and risk factors

a. Previous history of meningococcal infection? [ ] Yes [ ] No [ ] Unknown
b. Risk factor for meningococcal infection? [ ] Yes* [ ] No [ ] Unknown

*If yes, specify (medical condition, close quarters, college campus, daycare worker, military, living in proximity or recent travel to endemic area(s), etc.) below:

Clinical presentation of meningococcal infection

Indicate type of clinical presentation (√ check all that apply)and provide date of onset/diagnosis in DD-MON-YYYY format)

[ ] Primary bacteremia_____

[ ] Meningitis_____

[ ] Septic arthritis_____

[ ] Pneumonia_____

[ ] Cellulitis_____

[ ] Other (please specify infection type & diagnosis date):

3. Technical investigations

Was Neisseria meningitidis testing done?
[ ] Yes, provide details below [ ] No, diagnosis based on clinical purpura fulminans

Gram stain: date collected: _____
Specimen Source: [ ] blood _____ [ ] cerebrospinal fluid (CSF) [ ] Other (specify): _____
Result: [ ] Gram negative diplococci [ ] Negative [ ] Inconclusive [ ] Unknown [ ] Other:_____

Cerebrospinal fluid (CSF) Profile: date collected:_____
Appearance:_____ Pressure_____ mm H2O
Glucose:_____ mg/dL Protein:_____ mg/dL RBCs:_____ mm^3
WBCs:_____ mm^3 Lymphs:_____ % Polys:_____% Mono:_____%

Culture: date collected: _____
Specimen Source: [ ] blood _____ [ ] cerebrospinal fluid (CSF) [ ] Other (specify): _____
Result: [ ] Positive for_____[ ] Negative [ ] Inconclusive [ ] Unknown [ ] Other:_____

Other investigations (e.g., imaging, etc.): please provide details of additional investigations, including date of testing, results, and units of measurement as applicable.

4. Supplemental Culture Information

Antibiotic use prior to laboratory specimen collection?
[ ] Yes [ ] No [ ] Unknown
→ **If Yes:**
Antibiotic(s) administered (specify name or type of antibiotic given along with start and end dates of administration in DD-MON-YYYY format):

Was any susceptibility data available?
[ ] Yes [ ] No [ ] Unknown

If yes, please summarize results below *(e.g., Resistant, Susceptible, Intermediate, Unknown, Not resistant):*

Was the serogroup of *Neisseria meningiditis* identified [ ] Yes [ ] No [ ] Unknown
If Yes, please specify the serogroup: [ ] A [ ] B [ ] C [ ] W [ ] X [ ] Y [ ] Z [ ] Non-groupable
[ ] Other:_____

Based on the information provided, please select one of the following clinical case definitions (in CAPITAL letters below):

❑ **SUSPECTED**
__Clinical purpura fulminans in the absence of a positive blood culture; or
__Gram-negative diplococci, not yet identified, isolated from a normally sterile body site (e.g., blood or CSF)

❑ **PROBABLE**
Detection of N. meningitidis antigen
__ In formalin-fixed tissue by immunohistochemistry (IHC);
__ or In CSF by latex agglutination

❑ **CONFIRMED**
__Detection of N. meningitidis-specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., blood or CSF), using a validated polymerase chain reaction (PCR) assay;
or
__Isolation of N. meningitidis from a normally sterile body site (e.g., blood or CSF, or less commonly, synovial, pleural, or pericardial fluid);

Section E. Meningococcal Vaccination and Antibiotic Prophylaxis

Has the patient ever received a vaccine against meningococcal infection? [ ] Yes [ ] No [ ] Unknown

- **If No**, check the reason(s) the patient was not vaccinated:
  [ ] religious [ ] medical contraindication* [ ] philosophical objection
  [ ] patient/caregiver refusal
  [ ] unknown [ ] Other (specify): _____
  *If medical contraindication, please specify _____

- **If Yes,**

- Is meningococcal vaccination up-to-date according to country guidelines? [ ] Yes [ ] No [ ] Unknown
- Date of last dose of vaccine prior to event onset? __ _ - _ _ _ - _ _ _ _ (DD-MON-YYYY)

Antibiotic prophylaxis

Has the patient ever received antibiotic prophylaxis for meningococcal infection**?** [ ] Yes [ ] No [ ] Unknown

→ **If Yes,** specify antibiotic(s) administered (include name or type of antibiotic given along with start and end dates of administration in DD-MON-YYYY format):

Meningococcal initial/booster vaccination details:

Vaccine administered (Type)/ Vaccine name (e.g., MenACWY (conjugate) vaccine, MenB (recombinant protein) vaccine)	Indicate if Initial or Booster *Initial (I) or Booster(B)*	Date of vaccine administration (DD-MON-YYYY)

Section I. Event Outcome

Please indicate dates in DD-MON-YYYY format

Please indicate the outcome of the meningococcal infection event:

[ ] Recovered: Date of recovery _____

[ ] Not Recovered

[ ] Recovering

[ ] Recovered with sequelae:

Date of recovery_____

Please specify any sequelae:_____

Outcome of the meningococcal infection event (continued):

[ ] **Fatal** (*Please attach copy of autopsy report if performed*):

Cause of death_____Date of death _____

[ ] Unknown [ ] Lost to follow-up [ ] Follow-up refused

PLEASE PROVIDE ANY ADDITIONAL INFORMATION YOU FEEL WILL ASSIST US IN OUR EVALUATION OF THIS REPORT: (*e.g., relevant medical history, concomitant illnesses, concomitant medications, including start and stop dates as applicable)*

If unable to provide the above information, please provide us with the patient's treating physician and/or primary care physician so that we may further pursue our obligation to obtain follow-up information regarding this event:

Treating Physician	Primary Care Physician
_____	_____
Address	Address
_____	_____
Phone	Phone
_____	_____

Thank you for taking the time to provide this information.

Please sign below:

Name_____**Title**_____
Please Print

Signature_____

Date_____

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Prior to the launch of zilucoplan in each Member State, the MAH must agree about the content and format of the CAP and educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The CAP and educational program are aimed at further minimizing the important potential risk of meningococcal infection by reinforcing the key safety information available in the SmPC and the PIL.

The MAH shall ensure that in each Member State where zilucoplan is marketed, HCPs and patients/caregivers who are expected to prescribe/use zilucoplan are provided with/have access to the following educational materials:

- Guide for HCPs
- Patient Alert Card
- Patient/Carer Guide

Key messages of the additional risk minimization measures

1 GUIDE FOR HCPS:

- A concise introduction to zilucoplan and the purpose of the Guide for HCPs.
- The HCP should educate the patient/caregiver on the risk in the Guide for HCPs and ensure the patient/caregiver is provided with a Patient Alert Card and a Patient/Carer Guide.
- Key information on the important potential risk of meningococcal infection.
  - Treatment with zilucoplan may increase the risk of meningococcal infection
  - Emphasize requirement of meningococcal vaccination and potentially antibiotic prophylaxis and that meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infection
  - Inform HCPs on how to comply with the CAP to ensure that only patients who have been vaccinated against meningococcal infection have access to zilucoplan
  - Importance of monitoring for meningococcal infection and educate patients/caregivers on signs and symptoms of meningococcal infection and when to seek medical attention
  - Recommendation for measures to take in case of suspected meningococcal infection
- Emphasize importance to patients/caregivers that the Patient Alert Card needs to be carried at all times and to be presented to all HCPs.
- Reminding the need for and how to report suspected adverse reactions.

2 PATIENT ALERT CARD:

- A concise introduction to the potential risk of meningococcal infections with zilucoplan as C5 inhibitor.
- A warning message for HCPs, including in conditions of emergency, that the patient is using zilucoplan.
- Signs and symptoms of meningococcal infection and when to seek medical attention.
- The importance of carrying the Patient Alert Card at all times and presenting it to all HCPs.
- Contact details of the zilucoplan prescriber.

3 PATIENT/CARER GUIDE

- An introduction to zilucoplan treatment and a description of the correct use of zilucoplan including key information for safe self-administration.
- Zilucoplan may increase the risk of meningococcal infection.
- Requirement of meningococcal vaccinations (initial and booster vaccinations) and potentially antibiotic prophylaxis to minimize the risk of meningococcal infections. Emphasize that meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infection.
- A controlled access program is in place to ensure that only patients who have been vaccinated against meningococcal infection have access to zilucoplan.
- Signs and symptoms of meningococcal infection and when to seek medical attention.
- The importance of carrying the Patient Alert Card at all times and presenting it to all HCPs.
- Reminding the need for and how to report suspected adverse reactions.

4 VACCINATION REMINDERS FOR PRESCRIBERS

- Emphasize importance of an effective vaccination against meningococcal infection to minimize this important potential risk.
- Remind prescribers to verify and ensure that their patient’s vaccination against meningococcal infection is still current according to relevant vaccination guidelines.