14 September 2023
EMA/CHMP/439661/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zilbrysq

International non-proprietary name: Zilucoplan

Procedure No. EMEA/H/C/005450/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AChR	Anti-acetylcholine receptor
ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse events
AIC	Akaike information criterion
ALS	Amyotrophic lateral sclerosis
ANCOVA	Analysis of covariance
APA	Anti-PEG antibodies
ARDs	Adverse drug reactions
AUC	Area under the drug concentration versus time curve
AUC_{last}	Area under the plasma concentration-time curve from zero to last measure
AUC_{0-24}	Area under the plasma concentration-time curve from zero to 24 hours after administration
$AUC_{0-\tau}$	Area under the concentration-time curve at steady state over the dosing interval (from time zero to τ)
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
C5	Complement component 5
CBL	Change from baseline
CCK	Cholecystokinin
CHMP	Committee for Medicinal Products for Human Use
CI(s)	Confidence interval(s)
CL/(F)	(apparent) Clearance
CNS	Central nervous system
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CSP	Clinical study protocol
DDI	Drug-drug interaction
DSC	Differential scanning calorimetry
EFD	Embryofetal development
ePPND	Enhanced pre-postnatal development
ERCP	Endoscopic retrograde cholangiopancreatography
FT-IR	Fourrier transform infrared spectroscopy
GC-MS	Gas chromatography mass spectrometry
GD	Gestation day
HDPE	High density polyethylene
hERG	human ether-a-go-go-related gene

HI	Hepatic impairment
HPLC	High performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
ICE	Intercurrent event
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IMNM	Immune-mediated necrotising myopathy
IMP	Investigational medicinal product
IPD	Individual patient data
IVIG	Intravenous immunoglobulin
J2R	Jump-to-reference
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LS(M)	least squares (means)
LOCF	Last-observation-carried-forward
MAC	Membrane attack complex
MAH	Marketing authorisation holder
MAR	Missing at random
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
(g)MG	Generalised myasthenia gravis
MG-ADL	Myasthenia gravis activities of daily living
MGC	Myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL15r	Myasthenia Gravis-Quality of Life 15-item scale revised
MGTX	Myasthenia gravis patients receiving prednisone
MMRM	Mixed model with repeated measures
(m)ITT	(modified) Intent-to-treat
MTP	Multiple testing procedure
NAb	Neutralising antibodies
NHP	Non-human primate
NMJ	Neuromuscular junction
NMR	Nuclear magnetic resonance
NOAEL	No-observed-adverse-effect level
NOR	Normal operating range
OLE	Open label extension
OR	Odds ratio
OX	Orexin

PAR	Proven acceptable range
PB	Placebo
PBT	Persistence bioaccumulation and toxicity
PD	Pharmacodynamic
PDE	Permitted daily exposure
PEG	Polyethylene glycol
PFS	pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PLEX	Plasma exchange
PNH	Paroxysmal nocturnal haemoglobinuria
PP	Polypropylene
PT	Preferred term
popPK	population Pk
Q	Intercompartmental CL
QMG	Quantitative myasthenia gravis
QSAR	Quantitative structure–activity relationship
QTcF	QT corrected using the Fridericia method
QTPP	Quality target product profile
QWBA	Quantitative whole-body autoradiography
(s)RBC	(sheep) Red blood cell
RH	Relative humidity
RMP	Risk management plan
RNS	rigid needle shield
RP-HPLC	Reverse phase high performance liquid chromatography
SAD	Single-ascending dose
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SPPS	solid phase peptide synthesis
t_{max}	Time to maximum plasma concentration
$t_{½}$	Terminal half-life
TEAEs	Treatment-emergent adverse events
TGA	Thermo-gravimetric analysis
TK	Toxicokinetic

TMDD	Target mediated drug disposition
UTI	Urinary tract infection
UV	Ultraviolet
Vc(/F)	(Apparent) volume of distribution of the central compartment
Vp	Volume of distribution of the peripheral compartment
VPCs	Visual predictive checks
ZLP	zilucoplan

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma S.A. submitted on 31 August 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Zilbrysq, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

Product name Zilbrysq was designated as an orphan medicinal product EU/3/22/2650 on 2022-07-18 in the following condition: Treatment of myasthenia gravis.

The applicant applied for the following indication: the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and require treatment in addition to steroids or non-steroidal immunosuppressants.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) P/0143/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0143/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active substance status

The applicant requested the active substance zilucoplan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
29 May 2019	EMEA/H/SA/3949/2/2019/SME/III	*Professor de Andres Trelles, Dr Marion Haberkamp*
17 June 2019	EMEA/H/SA/3949/2/2019/SME/III clarification	*Professor de Andres Trelles, Dr Marion Haberkamp*
10 December 2020	EMEA/H/SA/3949/3/2020/I	*Ms Audrey Sultana and Dr Cristina Migali*

The protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

The applicant received scientific advice on the development of zilucoplan for treatment of generalised myasthenia gravis from the CHMP on 29 May 2019 EMEA/H/SA/3949/2/2019/SME/III and clarification on the 17 June 2019. The scientific advice pertained to the following pre-clinical development, Clinical development, Phase III, Methodology, Statistical Analysis, Safety.

The applicant received scientific advice on the development of zilucoplan for treatment of generalised myasthenia gravis from the CHMP on 10 December 2020 (EMEA/H/SA/3949/3/2020/I). The scientific advice pertained to the following quality aspects: starting materials, manufacturing sites, process validation for finished product.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	31 August 2022
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 December 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and	30 May 2023

PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 June 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	8 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zilbrysq on	14 September 2023
The CHMP adopted a report on similarity of Zilbrysq with Vyvgart and Soliris on (see Appendix on similarity)	14 September 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Myasthenia gravis (MG) is a rare disease characterised by the production of autoantibodies targeting proteins that are critical for the normal transmission of neurotransmitter signals from nerves to muscles.

2.1.2. Epidemiology

The prevalence of MG globally is estimated to be 12.4 (range 10.6 to 14.5) per 100,000 persons (Salari et al, 2021), hence, MG affects up to approximately 760,000 people worldwide. MG most commonly affects young adult women (under 40) and older men (over 60), but it can occur at any age. Epidemiological studies reveal an increasing prevalence over the past 50 years, due in part to an increase in the frequency of diagnosis in the elderly (Sanders et al, 2016). As the population has aged, the average age at onset has increased correspondingly.

The prevalence of MG in Europe (EU) is estimated to be 1 per 5,000 population (Orphanet).

2.1.3. Aetiology and pathogenesis

MG is an antibody-directed, complement-mediated autoimmune disease characterised by the production of autoantibodies targeting acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction (NMJ). Approximately 80% of patients with MG are acetylcholine receptor (AChR) antibody positive (Howard, 2018). In these patients, binding of anti-AChR auto-antibodies (mainly immunoglobulin [Ig]G1 and IgG3) to AChR results in uncontrolled and inappropriate activation of the classical complement pathway. The immune complex formed by the autoantibody-antigen complex activates the C1 component of the classical complement pathway. This leads to a series of enzymatic cleavage steps, culminating in the cleavage of complement component 5 (C5) into C5a and C5b and deposition of the cytolytic membrane attack complex (C5b-9, MAC) on the post-synaptic membrane of the NMJ and subsequent injury to the neuromuscular endplate, leading to failure of neuromuscular transmission.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

In approximately 15% of patients with MG, symptoms remain confined to the ocular muscles. In approximately 85% of patients, MG affects multiple muscle groups throughout the body, a condition that is typically referred to as generalised myasthenia gravis (gMG). Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Symptoms are typically at their mildest in the morning, when overnight inactivity enables replenishment of acetylcholine levels in presynaptic motor neurons and worsen during the course of the day. Muscle weakness can be localised to specific muscles, but often progresses to more diffuse muscle weakness (Gilhus and Verschuuren, 2015; Gilhus, 2016).

Generalised MG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalisation, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within 2 years of diagnosis (Shanker and Ramizuddin, 2014). The diagnosis of MG is based on medical history, evidence of clinical signs and symptoms, autoantibodies, electrophysiological studies (e.g, repetitive nerve stimulation, single fibre electromyography), imaging (e.g, computed tomography scan) and differential diagnosis with other neurological disorders including NMJ disorders (Gilhus et al, 2019).

2.1.5. Management

The most common target of autoantibodies in gMG is the nicotinic AChR, located at the NMJ, the point at which a motor neuron transmits chemical signals to a skeletal muscle fibre. Most therapies for gMG focus on either augmenting the AChR signal or non-specifically suppressing the autoimmune response. First-line therapy for symptomatic gMG is treatment with acetylcholinesterase inhibitors such as pyridostigmine. Although sometimes adequate for control of mild ocular symptoms, pyridostigmine monotherapy is usually insufficient for the treatment of generalised weakness, and dosing is often limited by cholinergic side effects. Therefore, in patients who remain symptomatic despite pyridostigmine therapy, corticosteroids with or without systemic immunosuppressants are used off label (Riedemann et al, 2002; Sanders et al, 2016). Immunosuppressants used frequently in gMG include azathioprine and mycophenolate mofetil. Cyclosporine, methotrexate, tacrolimus, cyclophosphamide, and rituximab are also used occasionally. These immunosuppressants have multiple established short- and long-term toxicities.

Well-controlled, randomised, efficacy studies for these agents are sparse, and these agents are not widely approved. Surgical removal of the thymus may be recommended in patients with non-thymomatous gMG and moderate to severe symptoms, in an effort to reduce the production of AChR autoantibodies (Wachtman and Mansfield 2012; Wolfe et al, 2016). Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are typically used short-term to manage worsening MG symptoms and in patients with myasthenic crisis or life-threatening signs such as respiratory insufficiency or dysphagia (Riedemann et al, 2002; Sanders et al, 2016). However, some patients with severe disease and multiple exacerbations may eventually require chronic IVIG or PLEX.

Inhibition of C5 for the treatment of gMG has already been shown to be effective in 2 clinical studies with the C5-blocking antibody, eculizumab (Howard et al, 2013; Howard et al, 2017), which established that inhibition of the terminal complement cascade by blocking cleavage of C5 is a clinically validated approach for treating gMG. Eculizumab is approved in the EU, Japan, and the US for treatment of adult patients with refractory gMG who are anti-AChR antibody positive. In addition, ravulizumab is approved in the US and EU for the treatment of adult patients with gMG who are anti-AChR positive (ravulizumab-cwvz; ULTOMIRIS® US Prescribing Information).

The most recent additions to the MG treatment regimen, with a new mechanism of action, has been the introduction of efgartigimod (Vyvgart®), an IgG1 Fc fragment that targets neonatal Fc receptor (FcRn), leading to reduced overall IgG recycling.

A large population of patients with MG with high unmet medical need and severe disease burden exists despite standard of care therapies (Cutter et al, 2019); this may be because of poor efficacy of existing agents; inability to receive adequate standard of care therapies due to adverse effects; perceived or actual high treatment burdens; or denial of access to a specific treatment by insurance companies due to its high cost. The high unmet medical need for new therapies due to insufficiencies of current treatment options continues to be strongly felt by the MG patient community as well. Based on these considerations, a high unmet medical need continues to persist for improved therapeutic options, and in particular a more accessible and convenient C5 inhibitor such as zilucoplan for patients with gMG.

2.2. About the product

Zilucoplan (ZLP) is a 15-amino acid macrocyclic peptide complement inhibitor designed for the treatment of conditions in which inappropriate activation of C5 has been demonstrated to play a role. Zilucoplan has been developed for the treatment of gMG in adult patients who are anti-AChR antibody positive.

Zilucoplan is provided as a single-use prefilled syringe with a needle safety device and is formulated as a sterile, preservative-free solution administered via SC injection. 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 which results in a downregulation of the assembly and cytolytic activity of the membrane attack complex (MAC). Additionally, by binding to the C5b moiety of C5, zilucoplan sterically hinders binding of C5b to C6, which prevents the subsequent assembly and activity of the MAC, should any C5b be formed.

The initially proposed indication was the following:

- For the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and require treatment in addition to steroids or non-steroidal immunosuppressants.

The proposed posology is weight-based and is 16.6 mg (<56 kg), 23.0 mg (≥56-<77 kg) or 32.4 mg (≥77 kg) of zilucoplan given as daily subcutaneous injection. This corresponds to approximately 0.3 mg/kg (effective dose 0.2-0.4 mg/kg depending on the weight band). The proposed posology with flat

dose within weight bands has been studied in the clinical programme and it is what is meant when a dose of 0.3 mg/kg is referred to.

2.3. Type of application and aspects on development

The clinical development programme for zilucoplan in patients with gMG and acetyl choline receptor antibodies includes three clinical studies, MG0009 (phase II), MG00010 (RAISE) and MG00011 (RAISE-XT). Further, a model-informed analysis was submitted to estimate the maintenance of efficacy effect versus placebo.

Scientific advice and protocol assistance were provided as the following procedures: EMEA/H/SA/3949/1/2018/PA/SME/III, EMEA/H/SA/3949/2/2019/SME/III, EMEA/H/SA/3949/3/2020/I, EMEA/H/SA/3949/2/2019/SME/III (Clarification letter), and a national scientific advice in November 2021 at the Swedish Medicinal products Agency. See above further details for centralised SA procedures.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection in pre-filled syringe in three different dose presentations (16.6 mg, 23.0 mg and 32.4 mg) with zilucoplan as active substance. The product contains the sodium salt.

Other ingredients are sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride and water for injections.

The product is available in a prefilled syringe (type I glass) with a 29G ½" thin wall needle closed with a grey fluoropolymer laminated bromobutyl rubber plunger stopper. The needle is protected with a rigid needle shield consisting of a thermoplastic elastomer needle shield and a polypropylene rigid shield. Each prefilled syringe is pre-assembled with a needle safety device, a finger grip and a coloured plunger:

- Zilbrysq 16.6 mg solution for injection in pre-filled syringe - 0.416 mL solution for injection in pre-filled syringe with rubine red plunger:
- Zilbrysq 23 mg solution for injection in pre-filled syringe - 0.574 mL solution for injection in pre-filled syringe with orange plunger;
- Zilbrysq 32.4 mg solution for injection in pre-filled syringe - 0.810 mL solution for injection in pre-filled syringe with dark blue plunger.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of zilucoplan sodium is N^2-Acetyl-L-lysyl-L-valyl-L-α-glutamyl-L-arginyl-L-phenylalanyl-L-α-aspartyl-N-methyl-L-α-aspartyl-3-methyl-L-valyl-L-tyrosyl-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)-L-alanyl-L-α-glutamyl-L-tyrosyl-L-prolyl- (2S)-2-cyclohexylglycyl-N^6-(3-{ω[(N-hexadecanoyl-L-γ-glutaminyl)amino]-tetracosakis(oxyethylene)}-propanoyl)-L-lysine (6→1^6)-lactam, tetra sodium corresponding to the molecular formula $C_{172}H_{274}N_{24}O_{55}Na_4$.. The sodium salt has a relative molecular mass of 3650.10 and the following structure:

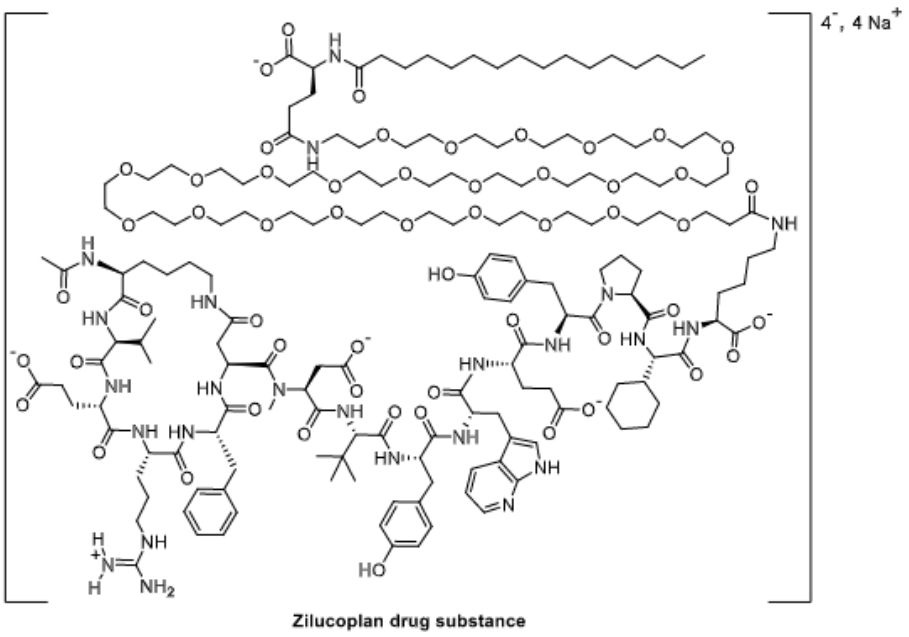


Figure 1: Active substance structure

Zilucoplan active substance is a synthetic peptide conjugated with an ethylene glycol moiety. The chemical structure of zilucoplan sodium was elucidated by a combination of spectroscopic evaluation and physical measurements including near UV spectroscopy, 1D- and 2D-NMR ($^{1}H/^{13}C/^{15}N$), GC-MS-based chiral amino acid analysis, amino acid analysis, MS sequencing, optical rotation and solubility. The higher order structure of the active substance was evaluated by techniques such as far UV circular dichroism spectroscopy, FT-IR spectrometry, fluorescence spectroscopy and differential scanning calorimetry (DSC). The solid state properties of the active substance were measured by x-ray powder diffraction, thermogravimetric analysis (TGA) and water vapor sorption.

The active substance is a white to off-white, low-density very hygroscopic powder. The aqueous solubility of zilucoplan undergoes a sharp transition from low to high solubility, across the iso-electric point, above pH 5.

Zilucoplan exhibits stereoisomerism due to the presence of 16 chiral centres, all located at the amino acid α-carbons and having L-configuration. Data provided from chiral amino acid analyses demonstrate low or undetectable amounts of D-amino acids indicating that zilucoplan active substance consists of L-amino acids. Stereochemical control is achieved by a combination of starting material selection (L-aa) and starting material specifications, and process design aiming at epimerisation suppression. The peptide synthesis contributes to impurity control, as do the capping procedures as well as chromatographic purifications and control of input material.

Polymorphism has not been observed for zilucoplan sodium. The solid form was analysed by X-ray diffraction and determined to be amorphous; the solid material was also characterised using DSC and TGA: the sample was heated from 25 to 250℃, no significant phase transition was observed.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is obtained from two manufacturers.

Zilucoplan consists of two major units: a cyclic peptide and an ethylene glycol moiety. In the final process steps, the cyclic peptide and the ethylene glycol moiety are conjugated, and the substance is thereafter purified and lyophilised.

1The proposed starting materials are found acceptable and in line with given scientific advice as well as ICH Q11 expectations. None of the proposed starting materials are claimed to be a commodity in a non-pharmaceutical context.

Critical process parameters and in-process controls are clearly described for the synthesis of zilucoplan. Adequate in-process controls are applied during the synthesis. The overall active substance synthesis includes four defined intermediates. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

No design space is proposed, and the manufacturing process is operated at target set-point or normal operating ranges (NOR) for all parameters. Set points/NORs have been defined for all relevant parameters. Variation of one parameter within a proven acceptable range (PAR), whilst keeping all other parameters at setpoint or within NOR, is considered acceptable for a given unit operation. During the procedure a major objection (MO) was raised requesting applicant to describe more clearly how the proposed reaction conditions and controls were established. In response, scientifically based justifications, supported by analytical batch data complying with relevant acceptance values, were provided. The identified CQAs are considered relevant for the active substance and were used to guide the process development in a rational way. The applicant has provided an acceptable presentation of the manufacturing process development, describing how in house experience and knowledge were combined with justified assumptions and experimental results to define and establish the process conditions. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The active substance is supplied as a non-sterile material.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The initial process 1.0 was further optimised to process 2.0 and then process 2.1. Changes introduced have been presented in sufficient detail and have been justified. The batch release, characterisation, and stability data demonstrate that the manufacturing sites, scale changes, and process improvements implemented during the development of the zilucoplan manufacturing process had no negative impact on the impurity profile and/or physico-chemical properties of zilucoplan active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in high density polyethylene (HDPE) bottles with polypropylene (PP) screw cap which complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual inspection), appearance in solution (Ph. Eur.), identity (MS, structural analysis, UHPLC), assay (liquid chromatography), water content (KF), sodium content (Ph. Eur.), purity (liquid chromatography), residual solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The specifications cover the expected tests for the active substance and ensure robust and consistent quality is obtained. Acceptable justifications for the compendial tests, water content, and sodium content are presented. Residual solvents used in the last process step are controlled at their ICH Q3C limits which is fully endorsed.

As the active substance is a synthetic peptide, Ph. Eur. monograph Substances for pharmaceutical use apply rather than ICH Q3A. During the procedure a MO was raised requesting toxicological data to be provided to support limits for other specified impurities above the qualification threshold as per the Ph. Eur. monograph for Substances for pharmaceutical use (≤ 1.0%). In response, the applicant presented interspecies data to toxicologically support the proposed specification limits for the specified impurities. The proposed limits have been acceptably qualified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Analytical data from a relatively large number of batches is presented, including batches made to early development process. The manufacturing process history is described in S.2.6, with adequate details.

- process 1.0, used during early development: Data from eight batches are presented; one of the batches was considered non-GMP.
- process 2.0: Data from six batches are presented.
- process 2.1: Data from twelve batches are presented.

It is clearly stated that each batch was tested and released according to the current specification at that time. In the dossier, data is consistently presented against the proposed commercial specification, with comments explaining deviations from acceptance criteria. Generally, the historical batches comply with the current limits. Any deviations are acceptably explained.

2.4.2.4. Stability

Stability data from 13 commercial scale batches of active substance from both the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 48 months under long term conditions (-20±5ºC), for up to 48 months under accelerated conditions (5±3°C) and for up to 48 months under accelerated conditions (25±2°C/60±5% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release, with the exception of identity, sodium content and residual solvents, which is acceptable as they are not stability indicating. The active substance is stable under the studied conditions. Assay and impurity levels remain stable in the included batches, and upon comparison between the batches, similar results are revealed.

Photostability testing following the ICH guideline Q1B was performed on two batches. Degradation of the active substance was observed under the conditions tested for samples exposed to direct light and for samples stored in primary packaging but were still within the commercial specification for purity and total impurities. No significant degradation of zilucoplan was observed for samples stored in both primary and secondary packaging confirming that the current packaging (i.e., primary and secondary) is suitable to protect zilucoplan active substance from photo-induced degradation.

Results on stress conditions: thermal stress, acid/base stress and peroxide stress were also provided on one batch. Based on available information, the analytical methods are accepted as stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. However, no retest period is accepted. Therefore, to ensure the quality of the active substance and finished product, the applicant should test the active substance according to approved specifications prior to each use in finished product manufacture. The quantity of zilucoplan needed for

finished product manufacturing will be calculated based on the assay from the active substance certificate (CoA). In the future, a variation can be submitted to introduce a retest period.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is supplied as a sterile, preservative-free solution in a 1 mL long Type I glass pre-filled syringe. Each single-use syringe contains zilucoplan active substance (40 mg/mL) in an iso-osmotic buffered solution. Other ingredients are sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride and water for injections.

The finished product is provided in 3 dose presentations (16.6 mg, 23.0 mg and 32.4 mg) accomplished by varying the syringe fill volume.

The pharmaceutical development is extensively described. Critical quality attributes (CQAs) were identified based on the quality target product profile (QTPP), knowledge of the zilucoplan active substance, and information gained during process development and manufacture.

All excipients are compendial grades. Anhydrous disodium phosphate (dibasic sodium phosphate anhydrous), sodium chloride and water for injection complies with respectively Ph. Eur. monograph. Sodium dihydrogen phosphate monohydrate (monobasic sodium phosphate monohydrate) complies with USP. All excipients are tested for bacterial endotoxins. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging consists of a single-use 1 mL long glass (Type I) syringe with a 29G, ½" thin wall needle. The syringe is closed using a fluoropolymer-laminated bromobutyl rubber plunger stopper and a rigid needle shield (RNS) consisting of a thermoplastic elastomeric needle shield and a polypropylene rigid shield. Each pre-filled syringe is preassembled with the safety syringe components.

A colour-coded plunger rod and carton will help differentiate each dose strength: rubine red for low, orange for medium and dark blue for high dose.

The same formulation (40 mg/mL) and the same pre-filled syringe has been used in clinical studies since Phase 1 except for the clinical study UP0112 where vials instead of pre-filled syringes were used. The manufacturing process was transferred for Phase 3 clinical studies. Sufficient data are provided demonstrating that both manufacturing sites are comparable and provide the finished product with consistent quality.

The commercial dose presentations (16.6 mg, 23.0 mg and 32.4 mg) are developed by varying the syringe fill volume to allow dose variation and a daily dose of 0.3 mg/kg. The commercial presentations are used in the clinical studies. In some Phase 2 studies additional dose presentations (6.0 mg, 8.8 mg and 12.4 mg) were also used to achieve the clinical daily dose of 0.1 mg/kg.

There is no overage, however, the pre-filled syringes are filled with a slight overfill in order to ensure that the nominal dose volume.

Extractables and leachables are sufficiently studied. None of the extractables or leachables detected is considered associated with any patient safety concerns.

A valid Notified Body Opinion (NBOp) is provided confirming compliance with relevant General Safety and Performance Requirements (GSPRs) set out in Annex I of Regulation (EU) 2017/745.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of following steps: dissolution of zilucoplan active substance in buffer solution, sterilisation, filling in pre-filled syringes and packaging.

The syringe, including needle and the rigid needle shield, is sterilised by the supplier. The plunger stoppers are sterilised by the supplier. The sterilisation methods for the primary container (syringe and plunger stopper) are sufficiently described.

Major steps of the manufacturing process have been validated by a number of studies. Process validation has been performed on five consecutive process performance qualification (PPQ) batches covering the proposed batch size.

The maximum filling time for the finished product solution into the syringes is sufficiently justified. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), identity (UV, UHPLC), assay (liquid chromatography), degradation products (liquid chromatography), visible particles (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and container closure integrity test (Ph. Eur.).

The specifications for the assembled safety syringes contain tests for: extractable volume (Ph. Eur.), shield removal force, maximum break-loose force, maximum gliding force, activation force, resistance to compression force, separation force, visibility of drug compartment and lock-out confirmation.

Release and shelf-life specifications for pre-filled syringes includes relevant test parameters. In addition, the final assembled safety syringes are tested for extractable volume and relevant functionality tests. The analytical methods are sufficiently described and validated.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 5 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 20 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability studies has been performed on all three dose presentations (16.6 mg, 23.0 mg and 32.4 mg) at long-term conditions (5°C±3°C), accelerated conditions (25°C±2°C / 60%±5% RH and 30°C±2°C / 75%±5% RH) and stressed conditions (40°C±2°C / 75%±5% RH). Forced degradation and photostability studies has also been performed.

Long-term data are provided for up to 42 months of clinical batches and up to 30 months of primary registration stability batches manufactured by the commercial manufacturer. All data complies with the finished product specification.

Stability data at stressed conditions support the storage conditions to keep to pre-filled syringes protected from light and that temperatures down to -20°C, which may occur during shipping, do not impact the finished product quality.

The provided stability data supports the proposed shelf-life of 3 years when stored in a refrigerator (2-8°C) and that the pre-filled syringes may be stored for a single period of maximum 3 months up to 30°C within the 3-years shelf-life as stated in sections 6.3 and 6.4 of the SmPC.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure two MOs, one on the active substance manufacturing process development and one on the toxicological qualification of specified impurity limits, were adequately addressed by the applicant (as discussed above). The claimed retest period was not agreed; therefore, the applicant should test the active substance according to approved specifications prior to each use in finished product manufacture. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Zilucoplan (occasionally referred to as RA101495) is a 15-amino acid macrocyclic peptide complement inhibitor designed for the treatment of conditions in which inappropriate activation of C5 has been demonstrated to play a role.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Zilucoplan exerts a rapid and strong association with C5 followed by a slow dissociation from the same. Zilucoplan inhibits cleavage of C5 into C5a and C5b, in a dose-dependent manner, measured by the inhibition of downstream MAC formation. Furthermore, this potency correlates with the potency to inhibit blood cell haemolysis, suggesting that the primary mechanism of zilucoplan for blocking complement-mediated haemolysis is through the inhibition of C5 cleavage. Zilucoplan inhibits downstream MAC assembly induced by the classical, alternative and lectin complement pathways.

The effects of zilucoplan *in vivo* are mainly assessed by analysis of inhibition of haemolysis; this haemolysis is a consequence of inhibition of C5b. In contrast, the inhibition of C5a has only been characterised *in vitro*.

Data shows that zilucoplan have the potential to be effective in patients with C5 R885H mutations (a polymorphism that results in the individuals having no activity of the C5 monoclonal antibody eculizumab).

Zilucoplan demonstrated similar potent inhibition of complement-induced red blood cell (RBC) lysis in serum and/or plasma from non-human primate and human. In samples from pigs the activity was >30 lower than cynomolgus macaque. Very weak activity was observed in rat (>150 times lower than cynomolgus macaque) and little to no activity was seen in other species such as mice, guinea pigs, dogs, or rabbits.

Three potential metabolites of special interest have been assessed for its activities, these being RA102758, RA103488, and RA106009. Results from haemolysis assays indicate that RA102758 exhibits minimal activity mediated by the activation of classical complement pathway as compared to zilucoplan. On the other hand, RA103488 and RA106009 inhibit complement-mediated haemolysis of erythrocytes when activated by either the classical or alternative pathway with similar half maximal inhibitory concentration (IC_{50}) values as zilucoplan in both complement pathways examined.

Plasma drug levels at or above 2.5 µg/ml in monkeys achieves >90% inhibition of haemolysis. At a dose of 4 mg/kg/day, haemolysis was essentially completely inhibited to below 1% throughout dosing and remained below 3% 48 hours after the last dose. This indicates a strong relationship between the concentration of zilucoplan in monkey plasma and haemolysis.

2.5.2.2. Secondary pharmacodynamic studies

Zilucoplan demonstrates weak binding to C4 and human serum albumin. Data also shows that zilucoplan has no binding to C3, C3d, C4, C5, C6, C7 or CA II. Biotinylated analogues of RA101495 selectively isolate complement C5 from human serum in pulldown experiments. These results demonstrate the selectivity of RA10495 binding to C5 in human serum.

At concentrations ~10-fold higher than the plasma concentrations expected in the clinical setting (30µM) RA101495 and RA102758 did not show agonist activity of a selection of peptide liganded G-protein coupled receptors including cholecystokinin 1 (CCK1), cholecystokinin 2 (CCK2), glucagon and secretin receptors. At concentrations ~3-fold higher than plasma concentrations expected in the clinical setting (10µM) RA101495 and RA102758 did not show antagonism of any of the receptors tested.

35 targets known to be associated with abuse liability were evaluated in binding assays at 30µM (zilucoplan) or 3µM (RA102758 and RA103488). The metabolites did not show any significant binding on any of the 35 targets. However, two targets were found to interact with zilucoplan, these being orexin-1 and GABA transporter. These two targets were further evaluated in a concentration-response was determined using binding assays (for both targets) as well as in functional assays (agonist/antagonist) for OX1. In binding assays, the IC_{50} of zilucoplan was 33µM for orexin 1 (OX1) and 11µM for the GABA transporter. In addition, zilucoplan exhibited an antagonistic activity on O receptors with an IC_{50} of 44µM, which is >1000-fold above the free plasma therapeutic concentration.

2.5.2.3. Safety pharmacology programme

The safety pharmacology of zilucoplan was investigated regarding both the central nervous (CNS)-, the respiratory- and the cardiovascular systems and the studies were GLP compliant.

CNS safety was evaluated as a part of the 4-week repeat toxicology study in cynomolgus monkeys. No neurological alterations observed following treatment with zilucoplan up to 4mg/kg/day, corresponding to maximum plasma concentrations of 65.7µg/mL for males and 62.8µg/mL for females (this study, 20074710, is assessed in toxicology section.).

Respiratory and cardiovascular safety was evaluated in a dedicated *in vivo* study where cynomolgus macaques (n=4/group) were administered with either 2 or 10 mg/kg zilucoplan (SC) 8 days after being injected with vehicle on day 1. The doses used should provide complete inhibition of C5 activity. 10 mg/kg should correspond to ~30-fold clinical exposure and approximately twice the exposure compared to high dose in the toxicology study. No finding relating to either electrocardiology, blood pressure, respiratory parameters, nor body temperature were noted. In addition, an *in vitro* human ether-a-go-go-related gene (hERG) study was also conducted. Zilucoplan did not inhibit hERG-mediated current at the maximum (and only) tested concentration of 300µM, corresponding to 1.07 mg/mL unbound drug, showing in contrast an increase in hERG-mediated current by 39.2±7.7%, versus hERG current inhibition of 0.4±1.2% (n=3) in the control.

Furthermore, electrocardiology was also investigated as part of the 4-, 13-, and 39-week GLP toxicology studies in cynomolgus macaques. In line with the results found in the dedicated safety pharmacology study, there were no zilucoplan-related electrocardiographic findings.

2.5.2.4. Pharmacodynamic drug interactions

Rituximab is used for treatment of gMG. One of the mechanisms of action for B-cell depletion by rituximab is through complement-dependent cytotoxic effect of rituximab. This complement-dependent cytotoxic effect of rituximab has a potential interaction with the C5 inhibitory effects of zilucoplan.

2.5.3. Pharmacokinetics

Pharmacokinetic studies and method validation

The pharmacokinetic (PK) profile of zilucoplan was characterised using both *in vivo* and *in vitro* studies. *In vivo* studies consisted of studies using Sprague-Dawley rats and cynomolgus monkeys.

Toxicokinetic (TK) profiles were characterised according to GLP in in repeat-dose toxicology studies conducted in rats (up to 4 weeks) and monkeys (up to 39 weeks) after daily SC administration, in a male fertility study and in a combined embryofoetal and enhanced pre-postnatal development (ePPND) study in monkeys for zilucoplan. No validation according to GLP standards have been provided for the TK characterisation of major metabolite.

For the detection of zilucoplan-related material in the whole body or in biological samples, [14C]zilucoplan was used and measured by liquid scintillation counting and autoradiographic techniques with quantitative imaging. In quantitative whole-body autoradiography (QWBA) study 16863 [14C] zilucoplan labelled on lipid/palmitoyl side chain; in QWBA study C18038, [14C] zilucoplan was labelled on the terminal lysine residue, adjacent to the polyethylene glycol (PEG)-lipid tail. Zilucoplan levels in plasma from rat and monkey were determined using protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometry analysis. The assays were sufficiently validated for intra- and inter assay accuracy, precision, linearity, quantification range and limit of quantification as well as storage stability. The ELISA method was used to detect anti-drug antibodies (ADA) in monkeys. The data validation data presented in AR6187 seem sufficient to adequately quantify ADA titres.

Anti-zilucoplan antibodies were evaluated in cynomolgus monkeys in the 4-, 13-, and 39-week toxicology studies and in the combined embryofetal and ePPND studies. ADA positive animals had sufficient exposure for Zilucoplan with no significant effect reported on PD parameters. However, the presence of APA has not been investigated.

Absorption

Plasma PK parameters of zilucoplan was investigated in male Sprague-Dawley rat and Cynomolgus monkey after a single IV, PO, or SC dose.

In rats, zilucoplan was very poorly absorbed after single PO, with a bioavailability of approximately 0.42%. Following SC administration in rats, the mean area under the plasma concentration-time curve from zero to last measure (AUC_{last}) and maximum plasma concentration (C_{max}) of the 1 mg/kg dose were calculated to be 10.02% and 11.6% of the 10mg/kg dose, respectively. Thus, exposures to zilucoplan seem dose proportional following single dose administrations from 1 -10 mg/kg. The mean time to maximum plasma concentration (t_{max}) ranged from 4.67 to 5.33h. The extrapolated area was low (1 mg/kg dose: 0.27% and 10 mg/kg dose: 0.12%).

SC single dose administration in monkeys resulted in a bioavailability ranging between 73-79% indicating good absorption following SC administration. In repeat dose studies in monkeys, exposures to zilucoplan were slightly less than dose proportional from 0.21 to 4.2mg/kg. Steady state was reached by Day 4 of dosing. Low accumulation was observed after 7-daily dosing of zilucoplan in monkeys as the area under the drug concentration versus time curve (AUC) ratio ranged from approximately 1.6- to 1.8-fold when administered daily, and when given every 3rd day even lower.

Distribution

Plasma protein binding capacity of zilucoplan and two predominant metabolites RA102758 and RA103488 was also investigated in rat, monkey, and human plasma. The results jointly indicate high protein binding of zilucoplan, RA102758 and RA103488, all three >99%. Zilucoplan was found to be predominantly in the plasma fraction and did not show significant distribution into the erythrocyte fraction.

The organ distribution studies in rat jointly show a rapid distribution of radioactivity and a slow decay with no significant distribution to melanin. Data point to a distribution to mainly kidney, but also to liver, lungs, trachea, GI-tract (mucosa and wall). Low placental penetration of zilucoplan was shown in an *ex vivo* model and was not affected by the presence of human C5 protein. However, transplacental transfer of metabolites, especially major metabolite RA102758, has not been evaluated. Although demonstrating

brain penetration of zilucoplan in monkey, the levels are far less than those observed in plasma (approx. < 250-fold lower). However, none of the metabolites seem to penetrate to brain.

Metabolism

The *in vitro* metabolic profile of zilucoplan was evaluated in rat, monkey, and human hepatocytes. Zilucoplan was stable in human and monkey plasma as no metabolite was detected after an up to 8-hour incubation. Hydrolysis was detected as the predominant metabolic pathway. Six metabolites were observed in monkey and human hepatocytes where no human unique metabolite was observed. In rat hepatocytes, no oxidation metabolites were detected, and parent drug remained as the major component in rat hepatocytes, along with seven hydrolysis metabolites. The *in vitro* studies indicate that the monkey, in terms of the metabolite profiles, qualifies as a good species to investigate efficacy and safety where both metabolites of potential interest, RA102758 and RA103488, are present.

RA103488 is a ω-oxidation product of zilucoplan. This metabolite is present of monkey and humans, but not in rat. Pharmacologically it has similar activity as zilucoplan. However, RA103488 is representing 9.4% AUC of zilucoplan in human plasma, and therefore it is agreed that RA103488 is not considered to contribute substantially to the overall pharmacological activity.

RA102758 is a hydrolysis product of zilucoplan and is considered a major metabolite in humans and is present in humans, monkeys, and rats; however, it does not have a pharmacologic effect on the complement system and demonstrated no affinity for the C5 binding site occupied by zilucoplan.

Other than RA102758 and RA103488, RA103933 (a ω-oxidation product of RA102758 or hydrolysis product of RA103488) is the only metabolite with AUC near or above 10% of parent AUC in monkey plasma; however, data shows that the exposure of RA103933 was below 2.5% of zilucoplan AUC in human plasma following the last administration of once-daily dosing at 0.2mg/kg for 7 days. Therefore, RA103933 is considered as a minor metabolite in human, and it is agreed that no further studies are needed for this metabolite.

In liver, zilucoplan levels were dose dependent and compared to plasma levels, liver values ranged from 0-14% of plasma levels. Low levels of parent drug were observed in bile collected at terminal sacrifice, suggesting that this is not a major route of elimination of the parent drug. In contrast, RA1012758 was found at high concentrations in the bile, consistent with this being a major route of elimination for the metabolite.

Excretion

Hepatobiliary excretion played an important role in the elimination of drug-derived radioactivity from rat (~17% in faeces), with less found in urine (~9%). It was further confirmed that the remained radioactivity in rat tissue was related to radiolabelled palmitic acid, indicating the likely incorporation of this moiety into the endogenous metabolic cycle. However, in study C18038, the main excretion route of radioactivity was through urine (~50% of total radioactivity). The difference between these studies is explained by the fact that in study 16863, labelling was done on the lipid side chain, whereas in study C18038 zilucoplan was labelled in the lysine moiety. The difference between the above two studies is due to the ^{14}C labelling position and the involvement of labelled moieties in different endogenous metabolic cycles and the associated elimination route. When labelled on the lysine residue, more radioactivity was excreted in urine, which in turn seems reasonable considering that lysine is commonly excreted this way.

2.5.4. Toxicology

The toxicology programme conducted for zilucoplan includes SC repeat-dose toxicology studies in rats and cynomolgus macaques, a battery of genotoxicity assays, reproductive and developmental toxicology studies in cynomolgus macaques, and *in vitro* and *in vivo* safety pharmacology. 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. Adverse effects were observed in monkeys at subtherapeutic exposure. In common for many of the observed pathologies in various locations were vesicular degeneration of epithelial cells and mononuclear cell infiltrates in surrounding tissues. The applicant suggests that all, or most, test-article related findings in the repeat-dose toxicity studies in cynomolgus monkeys are attributed to opportunistic infection, but no direct evidence is provided, and a clinical relevance cannot be dismissed.

2.5.4.1. Single dose toxicity

No single-dose toxicity studies were conducted with zilucoplan. However, in the safety pharmacology study a single dose at 10mg/kg was well tolerated in cynomolgus macaques. No adverse effects or injection site findings were reported.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity of zilucoplan was evaluated in one 4-week study in rats and three studies in cynomolgus macaque (4-, 13-, and 39-weeks). As the pharmacological effect of zilucoplan is very week in rats compared to humans and non-human primates, the studies in cynomolgus are considered to be of most pharmacological relevance. In rats, zilucoplan-related findings were mainly limited to the injection sites. However, findings of increased fibrinogen, reticulocytes, and neutrophiles in rats given 40 mg/kg/day, together with a significantly decreased food consumption in rats given ≥10 mg/kg/day, may be suggestive of a systemic effect of zilucoplan also in rats. Although the pharmacological activity of zilucoplan is weak in this model (>100 times lower than in cynomolgus macaque and humans), a longer rat study may have revealed potential off-target systemic toxicity.

In the cynomolgus macaque, the main findings in toxicity studies were epithelial mononuclear cell infiltrates and vesicular degeneration with associated secondary sequelae including epithelial erosions. These were present in several locations in various tissues and organs. Also, pancreatic and hepatobiliary events were observed, including pancreatitis and elevation of liver- and pancreas enzymes. The No-Observed-Adverse-Effect Level (NOAEL) was considered by the applicant to be 2 mg/kg/day in the 13-week study, which was also considered to be the highest tolerated dose in the 39-week study. At this dose, the mean area under the plasma concentration-time curve from zero to 24 hours after administration (AUC_{0-24}) was 541 ug.h/mL which gives an exposure margin of ~2.0 to the predicted AUC_{0-24} seen in the phase 3 clinical studies. However, the increase in liver and pancreas enzymes, pancreatic acinar degeneration, and immune cell infiltrations seen consistently in the cynomolgus studies, already at the lowest dose given, would suggest that a NOAEL cannot be established.

Pharmacologic inhibition of C5 and dose-dependency of toxicity findings

In all three repeat-dose toxicity studies in non-human primate (NHPs), complement activity was determined in plasma samples using an *in vitro* RBC lysis assay. All control samples exhibited high levels of haemolysis, indicating no effect of the vehicle on complement activity. All animals treated with Zilucoplan (regardless of dose) showed high level of suppression of complement activity from within 2 hours post first dose throughout the entire duration of the studies. The suppressive effect was high (>80%) already at the lowest dose of zilucoplan tested (0.25 mg/kg/day) and increased further with

increasing dose (>90% suppression in the 1 and 2 mg/kg/day groups, and >95% suppression in the 4 and 6 mg/kg/day groups). Complement activity returned to baseline during the recovery in all groups. Many of the findings in the repeat-dose toxicity studies were not obviously dose-dependent. As the complement activity assay suggests almost full pharmacological activity of zilucoplan already at the lowest dose, the lack of a dose-response relationship may argue that such findings are secondary to C5 inhibition and opportunistic infection or other event preferably affecting animals with a supressed complement system. However, presence of inflammatory cells in multiple organs are dose-dependently increased in incidence and severity. Also other findings had a tendency to be more frequent in animals given the highest dose of zilucoplan. As nearly full C5 inhibition is achieved already at the lowest dose, findings caused by e.g. opportunistic infections would be expected to be equally common in all dose groups. Opportunistic infection is used by the applicant to explain most, or all, test-article related findings in the NHP studies, yet no attempts were made to identify any causative pathogens. In fact, the lack of clear changes in haematology parameters such as neutrophil or monocyte count may argue against frequent occurrence of opportunistic infection in zilucoplan-treated animals.

Mortality

Three cynomolgus macaque in the 39-week study were euthanised early due to developments attributed to zilucoplan. The primary causes of early euthanasia were multifocal skin erosions and ulcerations in two animals given 4 and 6 mg/kg/day, and colitis in one animal given the lowest dose (0.25 mg/kg/day). Although colitis was considered by the applicant to be a stress-exacerbated pre-existing condition, both this animal and the two additional early euthanised animals had histopathological findings in the pancreas of inflammation and acinar degeneration/degranulation (discussed in more detail below). Histopathological findings in the animal with colitis of decreased cellularity of the thymus, mild cortical hyperplasia of the adrenal gland, and moderate chronic atrophy of the adipose tissue of the heart epicardium are all in line with a chronic stress response that could have caused the colitis. Both animals euthanised early because of skin erosions had additional test article-related findings that contributed to their decline, e.g., liver fibrosis, lung oedema, mononuclear cell infiltrates and epithelial vesicular degeneration of several organs, and uterine endometrial degeneration. Pancreatic findings of acinar degeneration and inflammation in all three early euthanised animals (including the low dose monkey with colitis) is curious and mechanisms alternative to opportunistic infection cannot be excluded.

Clinical signs

Test article-related clinical signs were seen only in the 39-week study, and in three males given the highest dose (10 mg/kg/day) in the 13-week study, and included reddened skin (both local and generalised), ocular discharge and swelling in abdomen, penis, tail, or eyelid. These clinical signs were not clearly dose-related but affected a fraction of animals in all dose groups, which could be in line with an infectious aetiology. However, no attempts were made to identify any ongoing infection and alternative zilucoplan-related mechanisms behind the clinical signs are possible.

Pancreatic and hepatobiliary changes

In the NHP studies, signs of pancreatic and/or hepatobiliary toxicity were consistently reported. In the 4-week study, they were limited to minimally increased bile acids and lipase starting at 2 mg/kg/day. After 13 weeks of 10 mg/kg/day, one animal showed clear signs of pancreatitis including abdominal pain, acinar degeneration, and ductular hyperplasia and all animals had elevated liver and pancreas enzymes indicative of pancreatic and hepatobiliary toxicity. Mild degeneration of acinar cells was seen after 13 weeks also in two animals given 1 and 2 mg/kg/day respectively. In the 39-week study, minimally to mildly increased amylase and lipase was noted and considered Zilucoplan-related. Histopathologic findings were made in the pancreas of all three early euthanised animals and one additional animal in the 2.0 mg/kg/day dose group. In the 0.25 mg/kg/day dose group, the animal that was euthanised on day 245 due to weight loss and abdominal pain, in addition to colitis, showed moderate pancreatic

ductular degeneration/regeneration with acinar atrophy. The animals in the 4 and 6 mg/day/kg groups, euthanised for skin manifestations on days 52 and 203 respectively, were both found to have severe pancreatic and hepatobiliary changes: bridging portal fibrosis with biliary hyperplasia, portal mononuclear cell infiltrates, and oedema of the liver as well as pancreatic acinar degeneration with bridging fibrosis. The pancreatic events seen in all three studies in cynomolgus monkeys are of particular interest because elevated pancreas enzymes were noted also in the clinical studies and a few cases of pancreatitis were reported. A clinical relevance of the non-clinical findings cannot be dismissed but they call for a close follow-up of pancreatic events and epithelial degeneration post-approval.

Epithelial tissues

Epithelial mononuclear cell infiltrates and vesicular degeneration of epithelial cells were some of the main findings in the two cynomolgus studies of longer duration (13 and 39 weeks). After 13 weeks of 10 mg/kg/day zilucoplan, moderate vesicle formation in the mucosa of the tongue as well as rupture of the tongue epithelia were seen in two animals. In the 39-week study, vesicular degeneration that in some cases progressed to epithelial erosions were seen in epithelial tissues of tongue, oesophagus, cervix, and vagina. Similar vesicular degeneration and hydropic change of the epithelial cells of the skin, accompanied with epidermal erosion/ulceration, were seen microscopically in the skin lesions present at multiple locations on the body in the early euthanasia animals. Vesicular degeneration of epithelial cells at various locations on the body could be secondary to pathogen reactivation or de novo infection not translatable to humans. No skin infections have been observed in the clinical studies, and it is possible that differences in the background microbiome, stress, hygiene, etc between monkeys and humans can explain this difference. However, alternative zilucoplan-related mechanisms cannot be excluded as there is no direct evidence linking any pathogen to the observed findings.

Thymus

Lymphoid hyperplasia (described variously as lymphoid hypercellularity, increased lymphoid aggregates, or increased lymphoid follicles) was observed sporadically in the thymus of some animals in all dose groups already in the 4- and 13-week cynomolgus studies. In the 39-week study, lymphoid follicles were described as active secondary follicles indicative of an ongoing immune (B-cell) response. The applicant suggests that this is an adaptive immune response to opportunistic pathogen proliferation, colonisation and infection secondary to pharmacologic inhibition of C5, and that such infections are not directly translatable to human. However, there is no direct evidence linking any pathogen to the observed findings or to dismiss the clinical relevance and alternative zilucoplan-related mechanisms behind the thymic findings must be considered.

Uterus

In the 39-week cynomolgus study, mild endometrial degeneration was noted in one female given 1.0 mg/kg/day zilucoplan. In the animal in the 6.0 mg/kg/day dose group that was euthanised early for skin manifestations, endometrial degeneration was noted as marked, with loss of glandular mucosal structure replaced by loose fibrovascular stroma and mononuclear cell infiltrates.

Mononuclear cell infiltrates

Animals in all dose groups in the 13- and 39-week cynomolgus studies had inflammatory cells infiltrating the tissue in multiple organs (pancreas, kidney, tongue, oesophagus, salivary gland, thyroid, rectum, ileum, stomach, and urinary bladder). Although increased compared with control animals already at the lowest dose of 0.25 mg/kg/day, the incidence and severity of these infiltrates increased further with increasing dose. The applicant suggests that this finding is due to inflammation caused by opportunistic infections. However, as nearly full C5 inhibition is achieved already at the lowest dose, the clear dose-relationship in frequency and severity of mononuclear cell infiltrates may argue against that notion and alternative explanations must be considered.

2.5.4.3. Genotoxicity

Zilucoplan is not considered to have genotoxic potential. The genotoxic test battery consists of a bacterial reverse mutation tests (Ames), an *in vitro* mammalian chromosome aberration tests in human peripheral blood lymphocytes and *in vivo* genotoxicity testing utilising a rat bone marrow erythrocyte micronucleus assay. All assays were negative.

2.5.4.4. Carcinogenicity

No dedicated rodent carcinogenicity studies have been performed for zilucoplan, which is acceptable. A weight of evidence assessment concerning zilucoplan carcinogenic potential has been performed since the treatment is likely to be chronic. The weight of evidence discussion is based on non-clinical studies, available clinical data, and literature.

Zilucoplan was not genotoxic in standard genotoxicity studies, impurities were negative in quantitative structure–activity relationship (QSAR), and there were no pro-tumorigenic off-targets identified. There are two existing similar C5-related products that so far have not been linked to an increased carcinogenicity risk. The complement pathway is also not associated with tumorigenicity.

That being said, the two other products are of a different nature (monoclonal antibody versus small synthetic peptide) and dissimilar toxicity profile which makes such a direct product comparison difficult. Mild vesicular degeneration/hyperplasia of epithelial cells was noted in several tissues in the monkey repeat-dose toxicity studies. These findings are of uncertain clinical relevance provided that they could possibly be influenced by monkey specific infections.

However, considering the totality of data included in the carcinogenicity weight of evidence, most notably the lack of genotoxic potential and hyperplasia ranging from mild to moderate in severity, there is a low concern for carcinogenic potential.

2.5.4.5. Reproductive and developmental toxicity

The reproductive and developmental programme for zilucoplan consists of an ePPND and a male fertility study, both performed in cynomolgus monkeys.

Fertility study in male cynomolgus monkeys

A male fertility study with zilucoplan was performed in sexually mature cynomolgus monkeys using SC administration which is the intended clinical route. The monkeys (n=6/group) were treated daily for 13 weeks, and a recovery period of 8 weeks was included for some of the animals (n=2/group). Dosing with the high dose (4mg/kg/day) resulted in approximately 7 times exposure margin when compared to clinical exposure.

Overall, zilucoplan was well tolerated with no mortalities or treatment related clinical signs. No clear effects on body weight development, clinical pathology and organ weights were reported. It can be noted that 1/6 males administered high dose showed a decrease of testicular size during the dosing phase and a reduced testicular weight at necropsy. Given that the testicular effects were seen in a single animal the relevance is uncertain.

Analysis of spermatogenic stages indicated complete spermatogenesis with all stages present in all dose groups but there were animals that were scored as having reduced spermatogenesis stages.

There were histopathological testicular changes observed in all dose groups when compared to control. Minimal to slight unilateral or bilateral degeneration/depletion of germ cells was seen in 4/6 monkeys in all zilucoplan dose groups (1, 2, or 4 mg/kg) and also present in recovery animals. This can be compared

to the study controls where none of the control animals (0/6) showed signs of germ cell changes. In 1/6 low dose and 1/6 high dose animal, minimal unilateral fibrosis was seen. Degeneration/depletion of germ cells in the testicular tubules was characterised by various combinations of tubular dilatation, tubular vacuolation, reduced height of germinal epithelium, reduced spermatogenesis stages, and tubuli with sertoli cells only. No testicular effects were reported in the repeat-dose toxicity studies. There were immunological changes within the thymus of high dose monkeys. Minimal overall decrease in number/distribution of CD3, CD4, and CD8+ T- cells, also seen in recovery animals, was evident in monkeys administered 4 mg/kg, but not at lower doses. This was coupled to various degrees of increase in the incidence and degree of thymic involution/atrophy/lymphoid depletion in high dose monkeys. No clear effects were noted in when it comes to CD20+ and CD45+ T-cells.

ePPND study in cynomolgus monkeys

Potential reproductive and developmental toxicity was evaluated in an ePPND study conducted in pregnant cynomolgus monkeys. Zilucoplan was daily administered subcutaneously (intended clinical route) with 1, 2 or 4 mg/kg. The study included a embryofetal development (EFD) part which used 4 pregnant females/group and a postnatal part with 16 pregnant females /group. The monkeys were dosed from gestation day (GD) 20 to 100 or to end of pregnancy. The pregnancy loss, embryofetal development, survival, growth, and postnatal development of the offspring were assessed up to post-partum Day 91±1.

Dosing with the high dose (4mg/kg/day) resulted in approximately 4,5 times exposure margin in maternal animals when compared to clinical exposure. Maximum complement inhibition of around 60-70% was already reached with the low dose on GD58 and similar levels of inhibition were observed on GD90 and GD142. Zilucoplan was not detected in maternal plasma or infant plasma on post-partum day 21 nor in the milk samples collected on post-partum on day 28. Given that no TK measurements were performed in prenatal animals or directly after birth, it is unknown whether placental passage occurred in the study. An *ex vivo* closed-circuit human placental transfer model (described in the PK section) suggested 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 10 µg/mL zilucoplan, corresponding to a therapeutic dose of 0.3 mg/kg. The relevance of the *ex vivo* placental transfer model to the human situation is unknown and it should be noted that it only investigated transfer of zilucoplan parent compound and not metabolites.

Prenatal losses: Increased prenatal loss was noted in zilucoplan-treated ePPND phase maternal animals (dosed GD 20 to delivery). Prenatal loss was noted for 1/16 (6.25%) control animals, 5/16 (31.25%) animals administered 1.0 mg/kg, 4/16 (25.0%) animals administered 2.0 mg/kg, and 5/16 (31.25%) animals administered 4.0 mg/kg. For the high dose group there was also an increase when compared to historical controls. The corresponding prenatal loss values for the EFD phase maternal animals (dosed to GD 100) were 0/4 (control), 0/4 (1mg/kg), 1/4 (25%, 2mg/kg) and 0/4 (4mg/kg). The applicant has provided data that support that the prenatal losses in the study controls in the ePPND part was unusually low when compared to historical control groups. This is acknowledged and given that there was no correlation with complement inhibition and that spontaneous pregnancy losses can be high and variable in cynomolgus monkeys, the increase in prenatal losses is most likely not clinically relevant.

Embryo-fetal effects: Reddening of some organs was observed in 1/4 fetuses of a low dose maternal animal and 2/4 fetuses from high dose maternal animals. The clinical relevance is unclear.

Kinked tails were seen in 0/4, 1/4, 0/3, and 2/4 fetuses at doses of 0, 1, 2, and 4 mg/kg/day, respectively. Skeletal fetal findings included a misaligning of vertebrae 53 to 54 in 1/4 fetuses of a low dose mother and a misaligning of the zygostyle (caudal vertebrae) in 2/4 fetuses of high dose maternal animals. Given that no skeletal findings were noted in the in the X-rayed postnatal groups, the findings are considered most likely not related to treatment.

Postnatal effects: The incidences of infant deaths in zilucoplan groups were within the normal range of the concurrent control and reference data. A heart finding, possible the cause of death, was reported in one of the high dose infants found dead on day 16. According to the historical background data of the test site, heart findings are rare (12 cases in 947 control fetuses/infants). The applicant still considers the heart finding to be incidental with no dose-relationship which is a poor argument in this case since the finding occurred in the high dose group and maximum complement inhibition was already seen with the lowest dose. That said, given that this a single case, the toxicological relevance is uncertain. Two infants of the group administered 1.0 mg/kg had shortened thumbs on both hands. This finding is considered incidental.

2.5.4.6. Toxicokinetic data

TX evaluation of zilucoplan has been performed in 4-week repeated dose in rats, and in 4-Week-, 13-Week-, 39-Week repeated dose studies, together with male fertility and ePPND studies, all of these in monkeys. Major metabolite RA102758 was measured in monkeys in the 4- and 13-week, but not in the 39-week repeat-dose toxicology studies.

In the 39 weeks repeat dose study in monkey, doses were approximately dose proportional. Furthermore, there were no signs of accumulation and there were no sex-related differences in the TK. Protein binding was similar between monkeys and humans, thus there is no concern whether free fraction or total exposure have been used for calculation of exposure margins. Dose proportionality was also shown in rats and in reproductive toxicology (fertility, EFD/ePPND) studies in monkeys.

Adverse effects were observed in monkeys at subtherapeutic exposure. Overall, exposure margins to human exposure levels were low in the toxicity studies. In monkeys, a daily dose of 1 mg/kg gave an exposure that was similar to the clinical AUC and adverse events were observed already in animals given 0.25 mg/kg/day.

2.5.4.7. Other toxicity studies

Impurities are mainly peptidic-like ethylene glycol-related oligomer impurities of zilucoplan or isomers of zilucoplan. Peptidic ethylene glycol structures are negative for mutagenicity based on QSAR. The specified impurities have been qualified in the non-clinical toxicity studies.

2.5.5. Ecotoxicity/environmental risk assessment

Zilucoplan $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a persistence bioaccumulation and toxicity (PBT) substance as log Kow does not exceed 4.5. Zilucoplan is not expected to pose a risk to the environment.

Table 1: Summary of main study results

Substance (INN/Invented Name): Zilucoplan (RA101495)			
CAS-number (if available): 1841136-73-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	*	-2,52	Potential PBT: No, <4,5
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< 4.5	not B
	BCF		not B

Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0,00162	μg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)			No

* It is noted that the submitted study report is not in line with relevant OECD technical guideline (e.g., OECD 107) but, however, since the data indicates a highly hydrophilic substance with a good margin to the nearest ERA action limit (log Kow >3), the study is considered adequate in this case.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The applicant has shown that zilucoplan has strong and dose-dependent binding to C5 and that it inhibits the cleavage of C5 into C5a and C5b, both K_D and IC_{50} in the low nM range. Markedly, a slow dissociation (K_d: $2.1x10^{-4}s^{-1}$) from C5 is observed.

Inhibition of cleavage of C5 correlates with complement-mediated haemolysis, and it is agreed that therefore haemolysis is used to measure the potency of the inhibition of C5 cleavage. When C5 is cleaved an assembly of MAC is initiated, which in turn kills the pathogen. The applicant shows that zilucoplan inhibits the formation of MAC regardless of whether it is classic, alternative or lectin that initiates cleavage of C5 in the complement system, also here with IC_{50} values in the low nM range. The effects of zilucoplan *in vivo* are mainly assessed by analysis of inhibition of haemolysis; haemolysis is a consequence of C5b activity. In contrast, the inhibition of C5a activity *in vivo* has not been demonstrated. There is a lack of *in vivo* data confirming that the C5 molecule cannot disintegrate over time and release C5a. The theorised role of elevated levels of active C5a in toxicological findings remains unclear.

Although not studied clinically, it is agreed that zilucoplan has the potential to be effective in patients with C5 R885H mutations. It also is agreed that the selection of cynomolgus macaque as test species for the safety studies is relevant.

The applicant has investigated off-target binding to various complement system components, peptide ligand G-protein coupled receptors and a battery of targets associated with addiction, all of these without any notable findings. Although a broader secondary pharmacological screen is missing, this lack of information is, considering the available clinical data, not a cause for further concern.

No concerns are noted regarding the safety pharmacology. An increased hERG current upon exposure to test article is noted, with unclear clinical relevancy. The assessment of the increase in hERG current is hampered by the lack of dose-response evaluation and the clinical relevance of this data is unknown. However, there is no general concern regarding hypothesised QT prolongation as this has been investigated *in vivo* without notable findings.

Pharmacokinetics

Validated methods according to GLP for the detection of zilucoplan can be found in the dossier.

There are no non-clinical measurements of anti-PEG antibodies (APA). Formation of APA could potentially reduce toxicity in the non-clinical species. Based on the absence of altered pharmacokinetic/dynamic activity and the absence of immune-mediated findings, the likelihood of an anti-PEG antibody-mediated reduction of toxic potential in the non-clinical toxicology studies is deemed to be low.

The monkey is considered the central animal model for evaluating safety *in vivo*. After SC administration in monkeys a bioavailability of ~70-80%, an approximate dose proportionality and some accumulation is shown. Steady state was reached after approximately 4 days.

Two QWBA studies was conducted; the difference between the studies is that radiolabelling was done at two different places - one on the palmitic acid and one on the lysine that joints the peptide with PEG. The organ distribution studies jointly show a rapid distribution of radioactivity and a slow decay with no significant distribution to melanin. Regardless of labelling site, there is a high distribution to mainly the kidney. The studies differ regarding retention in a few organs; in the study with palmitic acid labelling there is retention in fat and endocrine tissue, which seem reasonable for a fat chain. However, this is not found in the study with labelling on the lysine. On the contrary this study shows even higher levels and retention in the kidney, in line with what is expected for lysine excretion. However, since zilucoplan does not bind C5 in rats, there is some uncertainty about the distribution in a species where zilucoplan binds to its intended target.

It is agreed that it seems that metabolism plays a major role in zilucoplan elimination, as indicated by the low quantities in bile and urine. This is consistent with the findings where low levels of parent drug were observed in bile collected at terminal sacrifice, also suggesting that this is not a major route of elimination of the parent drug. As for the metabolite RA102758, data show that the primary elimination route is hepatobiliary. However, data is also indicating excretion of this metabolite through urine.

Toxicology

The applicant's suggestion that all, or most zilucoplan-related findings in cynomolgus monkeys are attributed to opportunistic infections is not supported by data or identification of any causative pathogens. In fact, the lack of clear changes in haematology parameters such as neutrophil or monocyte count may argue against common occurrence of opportunistic infection in zilucoplan-treated animals and alternative mechanisms behind the observed findings cannot be excluded. Consistently in the repeat-dose toxicity studies vesicular degeneration of epithelial cells and mononuclear cell infiltrates were noted in various tissues at clinically relevant exposure.

Of particular interest in the repeat-dose toxicity studies is the consistent finding of pancreas-related toxicity, especially since elevated pancreas enzymes were noted also in the clinical studies and a few cases of pancreatitis were reported clinically. The mechanisms behind this are not clear, but a role for direct cleavage and activation of C5 by extrinsic proteases, not typically associated with complement, cannot be excluded. In the protease-producing pancreas it is known that C5 can in some cases be activated by trypsin, and as a consequence of the increased plasma C5 concentration after zilucoplan treatment, increased C5a and C5b locally in the pancreas can be envisioned. However, the difficulties in identifying the exact mechanism(s) behind the observed pathologies beyond speculation are acknowledged.

Toxicokinetics

Generally, toxicokinetic evaluation has done adequately. However, major metabolite RA102758 was not measured the 39-week repeat-dose toxicology studies. Despite this, the risk of RA102758 accumulation or insufficient exposure in the 39-week repeat-dose toxicology is deemed low owing to similar AUC_{met}/AUC_{parent} ratios between the 4-week and 13-week monkey studies. Furthermore, based on plasma exposure of RA102758 metabolite (AUC_{0-24h}=1040 µg.h/mL) at the highest tested dose of 10mg/kg/day in the 13-week study, an exposure multiple of 38 was obtained compared to the human plasma exposure measured (AUC_{0-24h}=27.1µg.h/mL at 0.3mg/kg/day) which further indicates a low risk of insufficient exposure to RA102758 in the 39 week study.

Zilucoplan $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L, and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, zilucoplan is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Assessment of the non-clinical dossier of zilucoplan revealed no major objections to marketing authorisation. There are no objections to marketing authorisation from a non-clinical point-of-view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2: Summary of studies supporting the clinical pharmacokinetics of zilucoplan

Study number	Study objectives	Number of participants, dose levels	PopPK or PK/PD	PD	PK sampling/ immunogencity
Initial PK/Tolerability, Phase 1 studies					
UP0112 (RA101495-1001)	First-in-human study to evaluate the safety, tolerability, PK, and PD of single escalating doses of ZLP and multiple doses of ZLP administered once daily for 7 days	SAD: ZLP 0.05mg/kg (N=2) ZLP 0.1mg/kg (N=4) ZLP 0.2mg/kg (N=4) ZLP 0.4mg/kg (n=4) PBO (N=8) MD: ZLP 0.2mg/kg (N=4) PBO (N=2) Dose by BW	Yes	Yes Assays: sRBC lysis, total C5, MAC, CH50	Intensive/ADA
UP0113 (RA101495-01.102)	To evaluate safety and tolerability in healthy Japanese study participants and compared them with healthy Caucasian study participants	SD ZLP 0.1mg/kg: Caucasian (N=4) Japanese (N=4) SD ZLP 0.3mg/kg: Caucasian (N=4) Japanese (N=4) MD ZLP 0.3mg/kg Caucasian (N=6) Japanese (N=6) PBO Caucasian (N=4) Japanese (N=4) Dose by BW	Yes	Yes Assays: sRBC lysis, total C5, MAC	Intensive/NA
UP0093 (RA101495-02.101)	To study of the effects of supratherapeutic dose of ZLP on cardiac repolarisation in healthy adult study participants	ZLP 0.6mg/kg: Group 1 (N=32) PBO: Subgroup 2A (N=16) Subgroup 2B (N=17)	Yes	Yes Assay: Total C5	Intensive/NA

Study number	Study objectives	Number of participants, dose levels	PopPK or PK/PD	PD	PK sampling/ immunogencity
		Dose by BW			
UP0094 (RA101495-02.102)	To assess the PK profile of single-dose ZLP and its metabolites in study participants with moderate hepatic impairment and study participants with normal hepatic function	SD ZLP 0.3mg/kg: Moderate HI (N=8) Normal (N=8) Dose by weight bracket	Yes	Yes Assays: sRBC lysis, total C5	Intensive/NA
UP0114 (RA101495-03.101)	To assess the PK profile and safety of single-dose ZLP and its metabolites in participants with severe renal impairment and in participants with normal renal function	SD ZLP 0.3mg/kg: Severe renal impairment (N=8) Normal renal function (N=8) Dose by weight bracket	Yes	Yes Assay: Total C5	Intensive/NA
UP0115[b]	To evaluate the relative bioavailability, PD, safety, and tolerability of a single SC injection of ZLP at different administration sites	ZLP 0.3mg/kg Group A: Treatment Sequence 1: AC (N=4) Treatment Sequence 2: CA (N=4) Group B: Treatment Sequence 3: BD (N=4) Treatment Sequence 4: DB (N=4) Dose by weight bracket	Yes	Yes Assay: sRBC lysis	Intensive/NA
Phase 2 efficacy and safety studies in gMG					
MG0009 (RA101495-02.201)	To assess the safety, tolerability, and preliminary efficacy of ZLP in study participants with gMG	ZLP 0.1mg/kg (N=15) ZLP 0.3mg/kg (N=15) PBO (N=15) Dose by weight bracket	Yes	Yes Assay: sRBC lysis, total C5	Sparse/NA[c]
Phase 3 efficacy and safety studies in gMG					
MG0010 (RA101495-02.301)	To confirm safety, tolerability, and efficacy of ZLP in study participants with gMG	ZLP 0.3mg/kg (N=86) PBO (N=88) Dose by weight bracket	Yes	Yes Assays: sRBC lysis, total C5	Sparse/ADA
MG0011 (RA101495-02.302 **Ongoing study**	To evaluate the long-term efficacy, safety, and tolerability of ZLP in study participants with gMG	PBO/ZLP 0.1mg/kg/0.3mg/kg (N=5) PBO/ZLP 0.3mg/kg (N=90) ZLP 0.1mg/kg/ 0.1mg/kg/0.3mg/kg (N=12) ZLP 0.3mg/kg/0.3mg/kg (N=92)	Yes	Assays: sRBC lysis, total C5	Sparse/ADA

Study number	Study objectives	Number of participants, dose levels	PopPK or PK/PD	PD	PK sampling/ immunogencity
		Dose by weight bracket			

CH50=total haemolytic component; C5=complement component 5; MAC=membrane attack complex; sRBC=sheep red blood cell; ZLP=zilucoplan

[b] Treatment Sequence 1 (AC): Abdomen A at Treatment Period 1 followed by Arm at Treatment Period 2; Treatment Sequence 2 (CA): Arm at Treatment Period 1 followed by Abdomen A at Treatment Period 2; Treatment Sequence 3 (BD): Abdomen B at Treatment Period 1 followed by Thigh at Treatment Period 2; Treatment Sequence 4 (DB): Thigh at Treatment Period 1 followed by Abdomen B at Treatment Period 2.

[c] The assay used for ADA assessment was considered not fit for purpose.

2.6.2. Clinical pharmacology

Zilucoplan (ZLP, RA101495) is a new chemical entity, and the PK studies should thus aim at describing the absorption, distribution, metabolism, and excretion (ADME) characteristics and also to identify subgroups where an altered exposure can be expected based on the pharmacokinetic properties. Potential interactions should also be evaluated.

Zilucoplan is a synthetic peptide conjugated with an ethylene glycol moiety. Zilucoplan binds to C5 and is designed for the treatment of gMG. The proposed posology is weight-based and is 16.6 mg (<56 kg), 23.0 mg (≥56-<77 kg) or 32.4 mg (≥77 kg) of zilucoplan given as daily SC injection. This corresponds to approximately 0.3 mg/kg (effective dose 0.2-0.4 mg/kg depending on the weight band). The proposed posology with flat dose within weight bands has been studied in the clinical programme and it is what is meant when a dose of 0.3 mg/kg is referred to. Dose strength variation is accomplished by varying the syringe fill volume.

To support this marketing application, the PK of zilucoplan and its metabolites, RA102758 and RA103488, is investigated in 9 clinical studies. A numerous of *in vitro* studies is also performed. All PK studies were conducted according to GCP.

The qualitative and quantitative composition of the formulation used in first-in-man and all subsequent clinical studies has remained unchanged throughout the full development.

As a peptide, zilucoplan is expected to be degraded into small peptides and amino acids via catabolic pathways. CYP4F2 contributes to a minor part of the metabolism. One major metabolite, RA102758 (inactive), is evident in human plasma. RA103488 is an active metabolite, with a similar potency as parent compound, but its contribution to the overall efficacy is considered low.

2.6.2.1. Pharmacokinetics

Methods

Quantification of zilucoplan, RA102758 and RA103488

Total zilucoplan and its metabolites, RA102758 (major metabolite) and RA103488, were quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using validated methods in human K_2EDTA plasma, urine and faeces. Two different methods were used for analysis of the total plasma concentrations of zilucoplan (Method 1 was used in the single-ascending dose (SAD) and multiple-dose (MD) study, UP0112, and Method 2 was used in the in the other clinical studies). No cross-validation was performed between these two methods.

A validated LC-MS/MS method was also used for quantification of unbound zilucoplan in human K_2-EDTA Plasma: Phosphate Buffered Saline.

Immunogenicity

A tiered approach to detect ADA and APA was applied.

The development of an assay to detect neutralising antibodies (NAb) was unsuccessful as issues with C5 target tolerance could not be circumvented.

Three ADA methods were developed to optimise drug tolerance, and full validations were carried out for each method.

- The initial method employed to support UP0112 detecting human ADAs was a ligand binding assay with biotinylated zilucoplan as a capture reagent and use of a labelled detection reagent. This assay showed a limited drug tolerance of 5 µg/mL of zilucoplan at PC antibody levels of 100 ng/mL. Although adequate for study UP0112, the assay was subsequently found to have insufficient drug tolerance to accommodate expected therapeutic levels of zilucoplan.
- The second-generation assay, used for study MG0009 showed insufficient drug tolerance and results were not reported.
- A third-generation assay was developed for use in the Phase 3 clinical studies and consists of an immunoassay with upfront acid dissociation. Biotinylated zilucoplan was used for the capture and detection by use of a mixture of labelled reagents.

The APA assay consists of a immunoassay, similar to the 3rd generation ADA assay, with upfront acid dissociation, capture with, and detection with a mixture of labelled reagents.

Pharmacokinetic data analysis

Non-compartmental methods and population PK (popPK) analysis were used to evaluate the PKs.

Population pharmacokinetic modelling

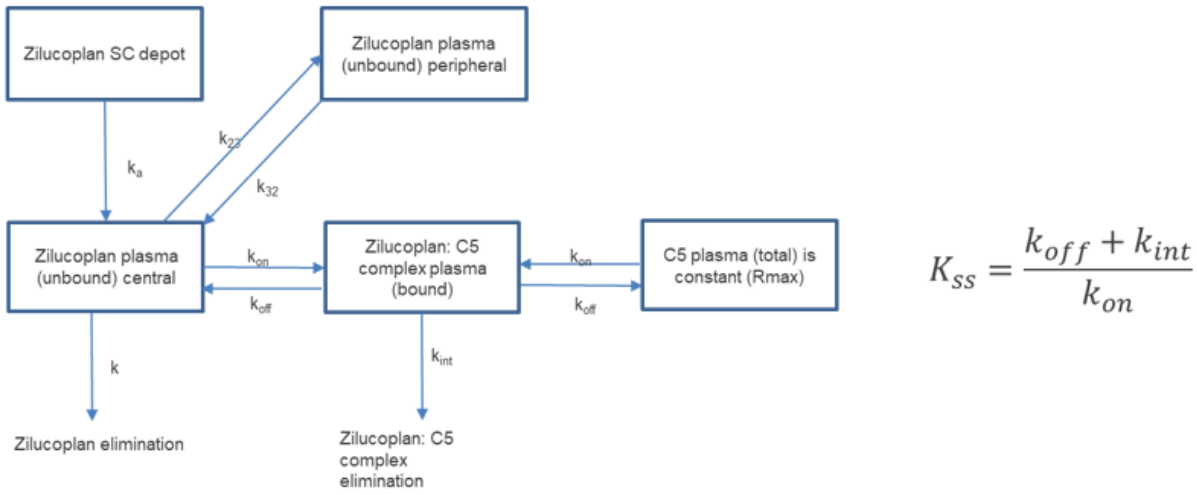
A popPK analysis was performed using PK data from studies UP0112 (SAD-MD), UP0113 (Japanese SD-MD), UP0114 (RI; only data from HV included in popPK analysis), UP0093 (TQT), MG0009 (gMG; Phase 2), and MG0010 (gMG; Phase 3).

Of the collected samples, 7.7% had a concentration below the limit of quantification and were excluded from the analysis. In total, 2174 zilucoplan concentrations from 200 individuals were used to fit the models.

A preliminary zilucoplan target mediated drug disposition (TMDD) population PKPD model had previously been developed using data from Phase 1 and Phase 2 studies (gMG patients and studies in paroxysmal nocturnal haemoglobinuria patients). The model was simultaneously fitted to zilucoplan and C5 complement concentration data and was considered too complex to be adequately supported by the sparse data collected in the Phase 3 study (MG0010). The preliminary model was therefore simplified by applying the quasi-steady-state approximation to the TMDD equations and by assuming a constant total (bound + unbound) C5 complement concentration in plasma. Thereby allowing the model to be fitted using only total zilucoplan concentration data.

The final popPK model is a 2-compartment model with first order absorption, followed by the simplified TMDD model (Figure 2). It includes estimated allometric coefficients to describe the effect of body weight on the linear zilucoplan PK parameters of clearance (CL), intercompartmental CL (Q), volume of distribution of the central compartment (Vc), and volume of distribution of the peripheral compartment (Vp).

Figure 2: Schematic description of the final zilucoplan population PK model



C5=complement component 5; PK=pharmacokinetic ; Rmax=maximum target density; SC=subcutaneous; ZLP=zilucoplan

A covariate analysis was performed to evaluate the potential effect of additional demographic covariates (age, sex, race, and population [healthy volunteers vs. gMG patients]) on CL and on the (constant) total C5 complement concentration (R_{max}; maximum target density). The effects of single covariates on the respective parameter were implemented in separate NONMEM models. Since the 95% confidence intervals (CIs) of the estimated single covariate effects were all including 1 (i.e., were not statistically significant at p=0.05), the base model, without additional covariates (body weight was included *a priori*), was considered the final model.

Parameter estimates for the final popPK model are presented in table below. The model was fitted using the FOCE estimation method with interaction in NONMEM (v. 7.5.0). Provided are also parameter estimates derived using sampling importance resampling, as implemented in Perl-speaks-NONMEM (PsN; v. 4.6.0), where the values correspond to the 50th (point estimate), and 2.5th and 97.5th (95% CI) percentiles of the estimated distributions.

Table 3: Parameter estimates for the final population PK model, derived using NONMEM and using sampling importance resampling, respectively

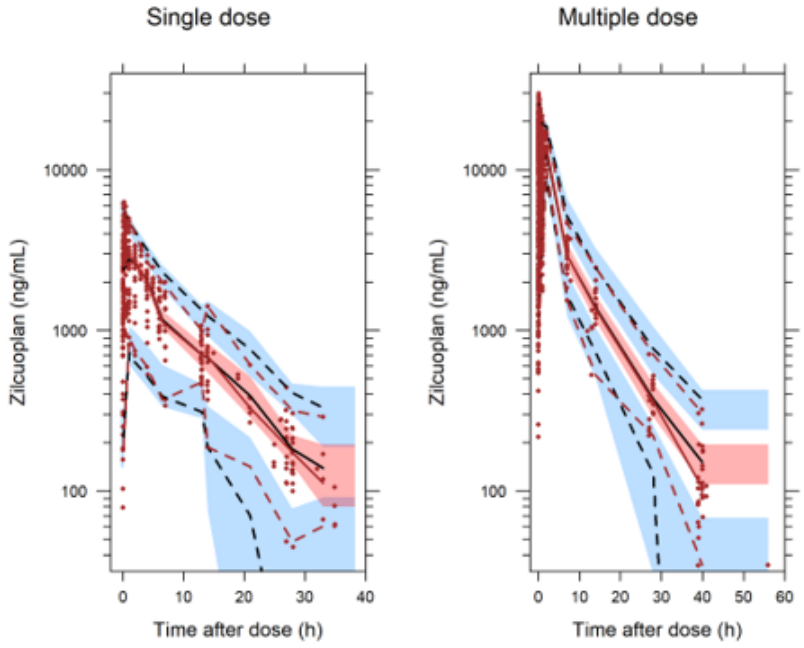
Parameter	NONMEM Estimate (95% CI)	NONMEM IIV	SIR Estimate (95% CI)	SIR IIV	Shrinkage[a]
ka (1/h)	1.22 (0.809/1.85)	41.5%	1.22 (0.939/1.66)	41.7%	29.6%
CL (L/h)	0.0845 (0.0815/0.0875)	16.8%	0.0845 (0.0817/0.0877)	16.8%	13.5%
Vc (L)	3.51 (3.31/3.71)	15.7%	3.51 (3.33/3.72)	15.8%	39.3%
Q (L/h)	0.566 (0.494/0.638)	39.4%	0.567 (0.488/0.647)	39.6%	58.7%
Vp (L)	3.45 (3.19/3.72)	0% Fixed	3.45 (3.17/3.75)		
Kss (ng/mL)	63.3 (13.4/113)	0% Fixed	62.4 (33.0/107)		
Kint (1/h)	0.00320 (0.00262/0.00379)	0% Fixed	0.00321 (0.00275/0.00363)		
Rmax (ng/mL)	1780 (1610/1960)	21.5%	1780 (1630/1980)	21.8%	49.4%
Allometric WT on CL and Q	0.715 (0.604/0.825)		0.716 (0.621/0.807)		
Allometric WT on Vc and Vp	0.452 (0.335/0.569)		0.454 (0.350/0.544)		
slope of logarithm of ka on WT	-1.01 (-1.38/-0.643)		-1.01 (-1.25/-0.783)		
Proportional RUV (%)	9.26 (8.41/10.1)		9.27 (8.85/9.64)		9.6%
Additive RUV (ng/mL)	63.3 (16.5/110)		64.0 (46.6/87.9)		9.6%

CI=confidence interval; CL=clearance; ka=absorption rate constant; IIV=inter-individual variability Kint=internalisation rate constant; Kss=quasi-stationary constant; OFV= objective function value; Q=inter 24%compartmental clearance; Rmax=maximum target density; RUV=residual unexplained variability; Vc=central volume; Vp=peripheral volume; WT=weight

a Shrinkage calculated using the standard deviation from NONMEM estimates

Goodness of fit plots and visual predictive checks (VPCs) were used to ascertain the ability of the final popPK model to adequately describe the observed zilucoplan concentrations. VPCs stratified by dose (not shown), by body weight (not shown), single and multiple dose (Figure 3), and population (HV/gMG patient; Figure 4) were provided. All figures demonstrate that there was adequate correspondence between the 2.5th, 50th (median), and 97.5th percentiles of the observed data and corresponding simulated quantiles for zilucoplan concentrations.

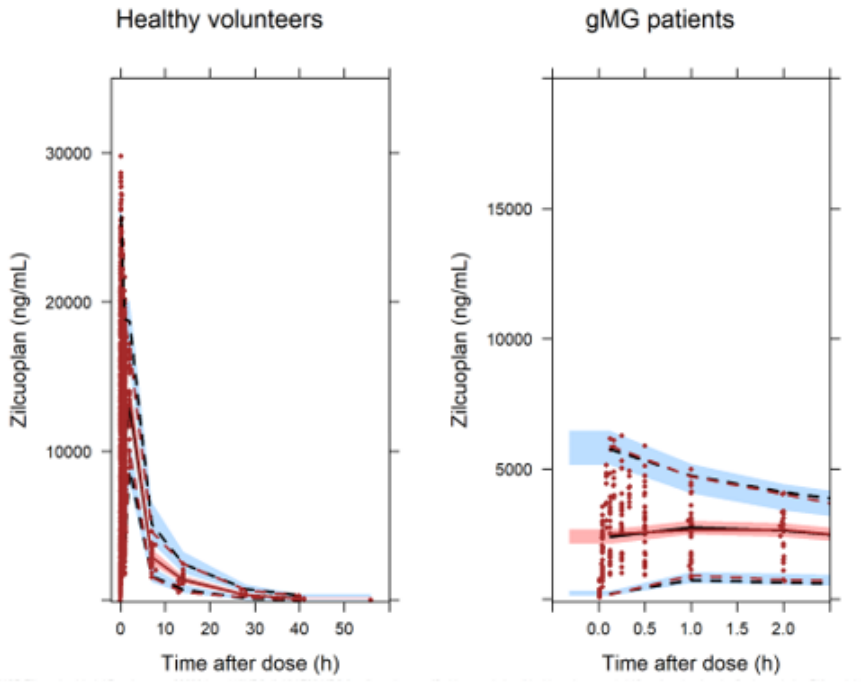
Figure 3: Visual predictive checks for the final population PK model for zilucoplan, stratified by single and multiple dose



popPK=population pharmacokinetic; VPCs=visual predictive checks; ZLP=zilucoplan

Red lines=observed ZLP quantiles (2.5th, 50th, 97.5th); black lines=median of ZLP (2.5th, 50th, 97.5th) across simulated trials; blue and red shaded areas=95% of the ZLP quantiles (2.5th, 50th, 97.5th) across simulated trials; red circles=observations

Figure 4: Visual predictive checks for the final population PK model for zilucoplan, stratified by population



popPK=population pharmacokinetic; VPCs=visual predictive checks; ZLP=zilucoplan

Red lines=observed ZLP quantiles (2.5th, 50th, 97.5th); black lines=median of ZLP (2.5th, 50th, 97.5th) across simulated trials; blue and red shaded areas=95% of the ZLP quantiles (2.5th, 50th, 97.5th) across simulated trials; red circles=observations

Absorption

C_{max} of zilucoplan is generally reached 3-6 hours after both single and repeated SC administration. Single dose PK in healthy volunteers are shown in Table 4.

Table 4: Pharmacokinetics of zilucoplan following a single SC injection of zilucoplan in healthy volunteers

Study no	**ZLP dose**	**ZLP PK parameter (geometric mean and geometric CV %)[a]**				
		C_{max} (ng/mL)	**t_{max}[a)] (h)**	**$AUC_{(0\text{-}last)}$ (h*ng/mL)**	**$AUC_{(0\text{-}inf)}$ (h*ng/mL)**	**$t_{1/2}$[a)] (h)**
UP0112	0.05 mg/kg, N=2	1010 (1.4)	4.5 (3, 6)	179,800 (1.8)	190,700 (1.6)	164 (156, 171)
	0.1 mg/kg, N=4	1540 (13)	3.0 (3, 24)	373,000 (13)	405,900 (14)	186 (178, 193)
	0.2 mg/kg, N=4	2958 (11)	4.5 (3, 48)	647,800 (17)	692,200 (20)	170 (144, 204)
	0.4 mg/kg, N=4	5860 (7.6)	4.6 (3, 6)	816,500 (14)	855,900 (15)	158 (139, 168)
UP0113	C: 0.1mg/kg, N=4	1700 (4.4)	3.0 (3.0, 3.0)	401,000 (4.7)	439,000 (6.2)	174 (7.4)
	J: 0.1mg/kg, N=4	1580 (14)	3.0 (3.0, 6.0)	428,000 (13)	480,000 (13)	201 (2.2)
	C: 0.3mg/kg, N=4	3580 (8.8)	6.0 (3.0, 6.0)	607,000 (21)	653,000 (23)	165 (11.8)
	J: 0.3mg/kg, N=4	3780 (5.1)	3.0 (3.0, 3.0)	737,000 (8.6)	808,000 (9.1)	183 (8.4)
UP0094	0.3 mg/kg, N=8	5128 (19)	8.0 (2.0, 12)	769,900 (13)	787,000 (13)	163 (111, 164)
UP0114	0.3 mg/kg, N=8	4830 (18)	4.0 (2.0, 12)	789,543 (18)	821,508 (20)	168 (150, 269)
UP0093[b)]	0.6 mg/kg, N=32	8372 (12)	4.0 (2.0, 8.1)	149,000 (9.3)	NC	--

Study no	ZLP dose	ZLP PK parameter (geometric mean and geometric CV %)[a]				
		C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{(0\text{-last})}$ (h*ng/mL)	$AUC_{(0\text{-inf})}$ (h*ng/mL)	$t_{1/2}$[a)] (h)
UP0115[c)]	0.3 mg/kg, N=16	**Group A: Abdomen (A) (N=7)**				
		5180 (13)	6.0 (3.0, 8.2)	821,700 (6.5)	858,200 (6.4)	181 (149, 203)
		Group A: Arm (C) (N=7)				
		5187 (18)	4.0 (3.0, 8.1)	806,300 (5.3)	841,300 (5.0)	183 (161, 198)
		Group B: Abdomen (B) (N=8)				
		5905 (18)	6.0 (3.0, 8.1)	903,400 (16)	942,400 (18)	178 (132, 219)
		Group B: Thigh (D) (N=8)				
		5103 (15)	6.1 (4.0, 24.0)	876,300 (16)	916,300 (18)	180 (123, 229)

CV=coefficient of variation; NC=not calculated; ZLP=zilucoplan
J=Japanese, C=Caucasian
[a] median (minimum, maximum) for t_{max} and $t_{1/2}$; in UP0113: geo mean and geo CV%

[b] Only data from the first day of treatment are shown

[c] Group A study participants received 1 injection in either the abdomen or arm in a randomised order. Group B study participants received 1 injection in either the abdomen or thigh in a randomised order.

Source: Modified Table 5-1 in clinical pharmacology summary

No bioequivalence study has been performed.

A study was performed to investigate the effect on different injection sites on the relative bioavailability of zilucoplan (UP0115, Table 4). The systemic exposures of ZLP, in terms of C_{max} and $AUC_{0\text{-}t}$, were comparable following a single SC injection in the abdomen as compared to the thigh and arm. No major differences in the geometric mean CL/F and $t_{½}$; and median t_{max} were noted between the injection sites. Based on visual inspection, the plasma concentration-time profiles of the metabolites seemed comparable between the injection sites.

Distribution

The apparent volume of distribution of the central compartment (Vc/F) of zilucoplan (not bound to target) is approximately 3.5 L (popPK analysis).

The plasma protein binding for zilucoplan was >99.8% (355-1, TR-0122). The two largest circulating metabolites in humans, RA103488 and RA102758, were also highly bound to plasma proteins (>99%) (355-1).

The blood-to-plasma ratios ranged between 0.70 and 0.76 (TR-0123) indicating that zilucoplan does not partition into erythrocytes.

Elimination

As a peptide, ZLP is expected to be degraded into small peptides and amino acids via catabolic pathways. CYP4F2 seems to contribute to a minor part of the metabolism.

The mean plasma $t_{1/2}$ of ZLP was approximately 172 hours (range: 139 to 204 hours) in healthy study participants. The mean apparent clearance (CL/F) ranged between 0.26 to 0.47 ml/h/kg after a single SC dose in the range 0.05-0.4 mg/kg. A higher mean CL/F of 1.33 ml/h/kg was reported after repeated administration of 0.2 mg/kg/day for 7 days. The popPK estimate of CL/F of drug not bound to target was 0.085 L/h (95 % CI: 0.082-0.088 L/h). Based on popPK analysis, there is no difference in CL/F between healthy participants and participants with gMG.

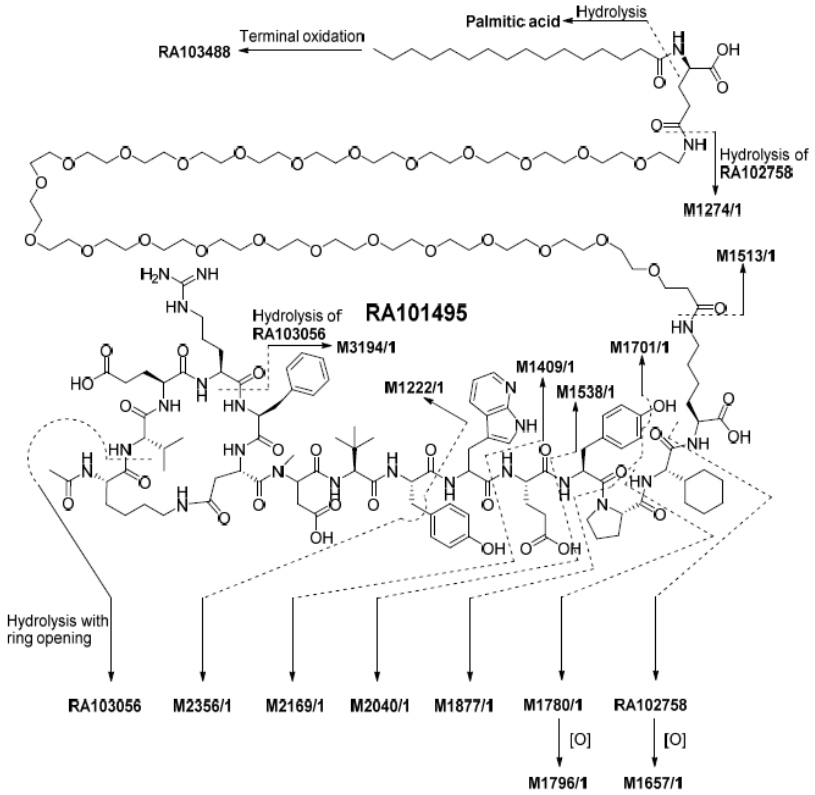
Excretion

No mass-balance study has been performed. Following a single dose injection of unlabelled zilucoplan, excretion of zilucoplan, RA103488, and RA102758 into urine and faeces appears to be minimal (studies UP0114 and UP0094).

Metabolism

The metabolism zilucoplan (RA101495) was investigated in *in vitro* studies with labelled ZLP and *in vivo* studies with unlabelled zilucoplan. The proposed metabolic pathways in human plasma are summarised in Figure 5.

Figure 5: Proposed metabolic pathways of zilucoplan in human plasma



Six metabolites (M2356/1, RA103056, M1780/1, M2040/1, M2169/1, RA102758) were identified in human hepatocytes, and no human unique metabolite was observed (16900). Peptide hydrolysis seems to be the predominant metabolic pathway. RA102758 was the abundant metabolite accounting for 28% and 7.2% of the total radioactivity in the 4-hr incubations with 1 and 10 μM [^{14}C]RA101495, respectively. M1780/1, M2040/1, and M2169/1 were co-eluted, accounting for approximately 31% and 13% of total radioactivity in the 1 and 10 μM incubations, in which the contribution of M2169/1 was 27% and 11% respectively.

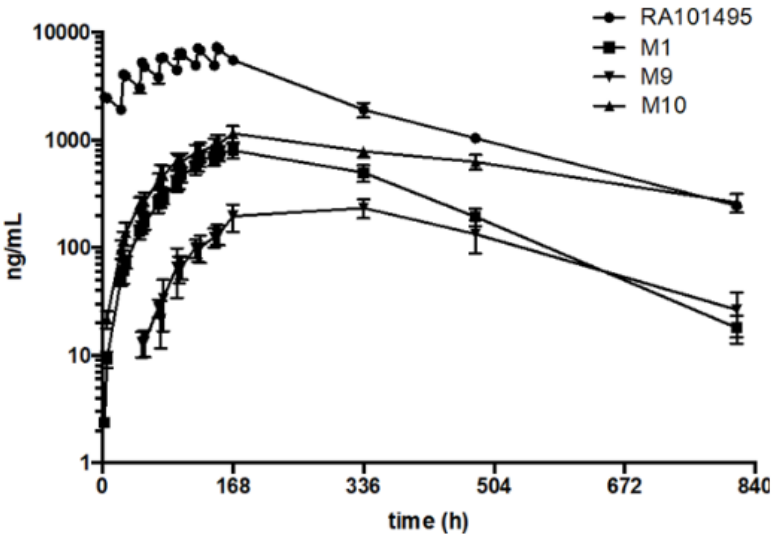
Metabolite identification was performed in pooled plasma samples collected 24-hours after dosing at week 12 from patients with gMG in the Phase 2 study, MG0009 (18512). In addition to RA101495 (zilucoplan), eighteen metabolites, including palmitic acid, were tentatively identified (Figure 5). RA106009 was not detected. The major metabolic pathways of RA101495 in human plasma involved: 1) proteolytic cleavage at different peptide bond in RA101495 and its mono-oxidation products; 2) mono-oxidation of RA101495 and its cleavage products; 3) amide hydrolysis at PEG linker.

In vitro studies with liver microsomes and recombinant CYP enzymes show that mainly CYP4F2 is involved in the formation of the active metabolite, RA103488 (ω-oxidation of RA101495) (TR-0160).

Pharmacokinetics of the metabolites

Potential metabolites were evaluated in the 0.4 mg/kg single dose cohort and in the 0.2 mg/kg multiple dose part of study UP0112 (TR-0128). Of those 10 metabolites evaluated, two larger metabolites RA103488 and RA102758 were identified in the single dose cohort. Thereafter, RA102758, RA103488 and RA103933 (observed in higher proportions in non-clinical studies), were quantified in the MD study (Figure 6). Based on molar units, the total plasma exposure (AUC_{0-24}) of RA102758 and RA103488 on the last day of treatment (day 7) were approximately 25% and 16% of parent $AUC_{0-24,}$ respectively. For RA103488 this metabolite-to-parent ratio was similar after the single as compared to repeated dosing, whereas for RA102758 the ratio was approximately 2-fold higher after repeated dosing. RA103488, is a pharmacologically active metabolite with a similar potency as parent compound *in vitro*, whereas RA102758 is not pharmacologically active.

Figure 6: Mean Plasma concentration vs time profile of ZLP (RA101495) and three metabolites during study of 7 daily subcutaneous doses at 0.20mg/kg



M1= RA102758, M9= RA103933, M10= RA103488 (study UP0112)

The PK of the metabolites were also studied after once daily SC injections of 0.3 mg/kg of ZLP for 14 days (UP0113). On day 14, the C_{max} of RA102758 (geometric mean range: 1270-1610 ng/mL) and RA103488 (geometric mean range: 889-1110 ng/mL) were reached approximately 13-23 hours and 2-15 hours after dosing, respectively. At approximate steady state (day 14), the metabolite-to-parent plasma area under the concentration-time curve at steady state over the dosing interval ($AUC_{0-\tau}$) ratios were approximately 25% for RA102758 and 10% for RA103488. The geometric mean (CV%) $t_{1/2}$ of RA102758 was estimated to 92 h (8.1%) and 108 h (9.3%) in Caucasians and Japanese subjects, respectively. The geometric mean (CV%) $t_{1/2}$ of RA103488 was estimated to 275 h (8.7%) and 288 h (6.1%) in Caucasians and Japanese subjects, respectively.

Following a single dose of 0.3 mg/kg to healthy subjects in the renal impairment study (UP0114), the mean $t_{1/2}$ of RA102758 and RA103488 were estimated to 107 hours and 301 hours, respectively.

Dose proportionality and time dependencies

Following single-dose administration of 0.05 to 0.4 mg/kg ZLP in the SAD study (UP0112), the increase in C_{max} was approximately dose proportional while the increase in $AUC_{0\text{-last}}$ and AUC_{inf} was less than dose proportional (Table 4).

When multiple doses of 0.6 mg/kg were given in the TQT study UP0093, a faster elimination was observed, however limited by short sampling times. Similar was observed in the 14-day study in Caucasian and Japanese participants (UP0113).

The accumulation ratio of zilucoplan was approximately 3 at doses of 0.2-0.6 mg/kg/dose (expressed as C_{max} and $AUC_{0\text{-}24}$ after a single injection as compared to repeated administration) (UP0093, UP0112, UP0113).

The terminal half-life ($t_{1/2}$) of ZLP was consistent following single and repeated dosing (0.2 mg/kg SAD mean $t_{1/2}$=172 hours [range: 144 to 204 hours]; 0.2 mg/kg MD mean Day 7 $t_{1/2}$=162 hours [range: 142 to 177 hours]). The Vz/F of ZLP increased with administration of MD of ZLP (0.2 mg/kg SAD mean Vz/F=71.4 mL/kg; 0.2 mg/kg MD mean Day 7 Vz/F=312 mL/kg). However, the Day 7 Vz/F for ZLP was still less than total body water, suggesting that ZLP does not distribute into the extravascular space upon repeat SC administration.

Immunogenicity

No positive ADA samples were observed in the multiple dose part of study UP0112, in which healthy participants were given SC injections of 0.2 mg/kg/day for 7 days.

Samples from studies MG0009 and IMNM01 are inconclusive due to poor drug tolerance of the second-generation assay.

ADA and APA samples were collected for all subjects in Phase III study, MG0010. Two study participants (of in total 86) in the ZLP 0.3 mg/kg treatment group were treatment-emergent ADA positive and had similar plasma concentrations of ZLP compared with ADA negative study participants. The ADA titres of these 2 study participants while treated with ZLP were 133 and 212.

Eight study participants were treatment-emergent anti-PEG positive. The titres of these participants while under ZLP treatment ranged between <100 (4 participants) and 1523.81 (one participant). Within this range 4 participants had titres between 100 and 750. Zilucoplan plasma concentrations of study participants who were anti-PEG positive were generally within the same range as the study participants who were anti-PEG negative, which includes n=5 baseline positive individuals.

The APA titres of the 2 additional study participants who became anti-PEG positive during MG0011 were low and close to the MRD. Combined ADA and APA data up to the MG0011 clinical data cutoff date of 08 Sep 2022 showing the number of participants that are ADA and APA positive are shown in Table 5.

Table 5: ADA and APA classification in studies MG0010 and MG0011 by treatment arm

ADA classification	Anti-PEG antibody classification (%)							
	a	b	c	d	e	f	g	Total
Placebo/ZLP 0.3mg/kg (N=90)								
Pre ADA neg – treatment induced ADA neg	53 (63.1)	13 (15.5)	0	4 (4.8)	2 (2.4)	0	0	72 (85.7)
Pre ADA neg – treatment induced ADA pos	2 (2.4)	2 (2.4)	0	1 (1.2)	0	0	0	5 (6.0)
Pre ADA pos – treatment reduced ADA	0	0	0	0	0	0	0	0
Pre ADA pos – treatment unaffected ADA	0	0	0	0	0	0	0	0
Pre ADA pos – treatment boosted ADA pos	0	0	0	0	0	0	0	0
Inconclusive	0	0	0	0	0	0	0	0
Missing	0	2 (2.4)	0	1 (1.2)	0	0	4 (4.8)	7 (8.3)
Total	55 (65.5)	17 (20.2)	0	6 (7.1)	2 (2.4)	0	4 (4.8)	84 (100)

ADA classification	Anti-PEG antibody classification (%)							
	a	b	c	d	e	f	g	Total
ZLP 0.3mg/kg/ZLP 0.3mg/kg (N=93)								
Pre ADA neg – treatment induced ADA neg	48 (58.5)	13 (15.9)	1 (1.2)	2 (2.4)	0	1 (1.2)	0	65 (79.3)
Pre ADA neg – treatment induced ADA pos	2 (2.4)	2 (2.4)	0	0	0	0	0	4 (4.9)
Pre ADA pos – treatment reduced ADA	0	1 (1.2)	0	0	0	0	0	1 (1.2)
Pre ADA pos – treatment unaffected ADA	0	0	0	0	0	0	0	0
Pre ADA pos – treatment boosted ADA pos	0	0	0	0	0	0	0	0
Inconclusive	0	0	0	0	0	0	0	0
Missing	0	2 (2.4)	0	0	0	1 (1.2)	9 (11.0)	12 (14.6)
Total	50 (61.0)	18 (22.0)	1 (1.2)	2 (2.4)	0	2 (2.4)	9 (11.0)	82 (100)

ADA=antidrug antibodies; neg=negative; pos=positive; ZLP=zilucoplan
Note Antidrug and anti-PEG antibodies data are not considered for MG0009 participants. Only MG0010 participants are summarised.
A Pre anti-PEG ADA negative-treatment induced anti-PEG ADA negative
B Pre anti-PEG ADA negative-treatment induced anti-PEG ADA positive
C Pre anti-PEG ADA positive-treatment reduced anti-PEG ADA
D Pre anti-PEG ADA positive-treatment unaffected anti-PEG ADA
E Pre anti-PEG ADA positive-treatment boosted anti-PEG ADA positive
F Inconclusive: participants who are ADA positive at baseline and some (or all) post baseline samples are missing, while other (if presesent) posttreatment samples are ADA negative
G Missing pre ADA negative (or missing) – more than postdose treatment samples are missing, while other (if present) posttreatment samples are negative.

Intra- and inter-individual variability

Following a single injection of zilucoplan in healthy subjects, the inter-individual variability (expressed as CV%) in C_{max} and AUC for zilucoplan were 1.4-19% and 1.6-23%, respectively. Based on individual parameter estimates from the popPK model, exposure metrics were derived for the gMG participants in the MG0010 study. These derived exposure metrics at steady state indicate an inter-individual variability (CV%) of 18-19% for C_{max} and AUC.

Pharmacokinetics in target population

The PK of zilucoplan and its metabolites, RA102758 and RA103488 were investigated in subjects with gMG. Relatively sparse PK sampling was use. PopPK analysis was used to derive population estimates of PK parameters and test the effect of various covariates. A brief summary of the systemic exposure in the studies in gMG patients are given below.

MG0009

This was a multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of ZLP in adult study participants with gMG. Forty-five study participants were enrolled in the study. Study participants were randomised in a 1:1:1 ratio to receive daily SC doses of ZLP 0.1 mg/kg, ZLP 0.3 mg/kg, or matching placebo. The first 12 weeks of the study (i.e., Main Portion) was placebo controlled. After 12 weeks, study participants in the placebo group were randomised to receive ZLP 0.1 mg/kg or 0.3 mg/kg and continued for an additional 12 weeks. The study was then extended for an additional 12 weeks, to have all study participants receive at least 24 weeks active treatment. At some point after 24 weeks, all participants in the 0.1 mg/kg dose group were switched to the 0.3 mg/kg dose group (i.e., Switchers). ZLP was provided in prefilled syringes for self-injection using weight bracketed dosing.

Approximate steady state plasma concentrations of ZLP, RA102758 and RA103488 were observed after 4 weeks of treatment. There was a trend towards an increase in geometric mean pre-dose plasma concentrations of RA103488 with time over the 24 weeks of treatment.

At week 12, the geometric mean (CV%) pre-dose plasma concentrations of zilucoplan were 5143 ng/mL (26%) and 10134 ng/mL (18%) in dose groups 0.1 and 0.3 mg/kg, respectively. The increase in pre-dose plasma concentrations were less than dose proportional.

At week 12 in the main study, for RA102758 the geometric mean metabolite-to-parent ratios of pre-dose plasma concentrations (based on molar concentrations) were 0.16 and 0.30 at doses of 0.1 and 0.3 mg/kg/day, respectively. The corresponding values for RA103488 were 0.11 and 0.13, respectively.

MG0010

This was a multicentre, randomised, double-blind, placebo-controlled study to confirm the efficacy, safety, and tolerability of ZLP in study participants with gMG. Study participants were randomised in a 1:1 ratio to receive daily SC doses of ZLP 0.3 mg/kg/day or placebo. The posology was the same as proposed in the SmPC. A total of 174 study participants were enrolled and 166 study participants completed the study. The total duration of study participation for all study participants was up to approximately 16 weeks, including a Screening Period of up to 4 weeks and a 12-week Treatment Period.

Pre-dose concentrations of zilucoplan and its metabolites, RA103488 and RA102758, were measured in plasma. ADAs and APA were also measured in the study (see section Immunogenicity).

Geometric mean pre-dose plasma concentrations of ZLP, RA103488 and RA102758 are shown in Table 6. Plasma concentrations of zilucoplan, RA103488 and RA10275, seemed to reach steady state after 4 weeks and remained relatively stable through Week 12.

Table 6: Geometric mean pre-dose (95% CI) plasma concentrations of ZLP, RA103488 and RA102758

	Geometric mean [95% CI] plasma concentration (ng/mL)					
Analyte	**Baseline**	**Week 1**	**Week2**	**Week 4**	**Week 8**	**Week 12**
Zilucoplan	5.1[a] [4.9, 5.2] (n=83)	11431 [10911, 11975] (n=81)	12460 [11879, 13071] (n=82)	12982 [12270, 13735] (n=79)	12433 [11767, 13137] (n=77)	12545 [11922, 13200] (n=75)
RA103488	5.0 (n=83)	1055 [982.5, 1133] (n=81)	1407 [1318, 1503] (n=82)	1553 [1449, 1664] (n=79)	1554 [1441, 1677] (n=77)	1554 [1444, 1673] (n=75)
RA102758	5.0 (n=83)	1072 [997.5, 1152.5] (n=81)	1694 [1572, 1825] (n=82)	2012 [1859, 2178] (n=79)	1891 [1735, 2060] (n=77)	1866 [1711, 2034] (n=75)

Note: Values BLQ are replaced by value of LLOQ/2 (=5 ng/mL) in calculations of the mean
n=number of subjects

[a] Measurable plasma concentrations were only observed in one subject

MG0011

MG0011 is an ongoing, multicentre, open label extension study evaluating the long-term safety, tolerability, and efficacy of zilucoplan in study participants with gMG who previously participated in studies MG0009 and MG0010.

Study participants receive zilucoplan 0.3 mg/kg administered SC at the Day E1 Visit. Single-use, prefilled syringes in injection devices are provided for use during the study, using weight-bracketed dosing. At the time of the clinical cut-off date (18 Feb 2022), 199 study participants were enrolled. Sparse sampling for PK was collected during the study. The concentrations of zilucoplan, RA103488 and RA102758 were measured in plasma.

Geometric mean plasma concentrations of zilucoplan in the 0.3/0.3 mg/kg treatment group were stable from baseline through Week E24. Geometric mean plasma concentrations of zilucoplan in the PBO/0.3 mg/kg treatment group reached steady state by Week E4, following 4 weeks of daily zilucoplan 0.3 mg/kg treatment, and remained stable up to Week E24. A similar pattern was observed for the metabolites, RA102758 and RA103488. The steady state pre-dose concentrations of zilucoplan and its metabolites seem to be in the same range as in study MG0010.

Special populations

Impaired renal function

In study UP0114, the impact of severe renal impairment on the PKs of zilucoplan and its metabolites, RA103488 and RA102758, was investigated after single of 0.3 mg/kg zilucoplan. It was planned to determine unbound concentrations, however the bioanalysis of free concentration turned out to be infeasible.

The PK profile of zilucoplan following SC administration was generally similar between healthy study participants and those with severe RI. The exposure of zilucoplan was slightly decreased in subjects with severe RI compared to subjects with normal renal function. RA102758 point estimates indicated

decreased exposure in subjects with severe RI compared to subjects with normal renal function, the CIs were however wide.

The exposure of the active metabolite RA103488 in terms of C_{max} and $AUC_{0\text{-last}}$ was approximately 1.5-fold higher in subjects with severe RI compared to subjects with normal renal function. The area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-inf}}$) of RA103488 was approximately 1.4-fold higher in subjects with severe renal impairment compared to subjects with normal renal function. However, in view of the much lower exposure of RA103488 compared to the parent compound zilucoplan in absolute terms (C_{max} ~20x, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ ~6x to ~7x), the applicant expects the clinical impact of this increase in subjects with severe RI to be negligible.

Zilucoplan, RA103488, and RA102758 were minimally renally excreted in both the normal and severe renal impairment groups (<1% of dose in total across all analytes) (sampling time 120 hours).

Overall, the applicant considers that no dose adjustment based on PK is necessary in patients with renal impairment.

Impaired hepatic function

The PKs of zilucoplan was investigated after a single SC dose of 0.3 mg/kg in subjects with moderate hepatic impairment compared with study participants with normal hepatic function.

Overall, 3 study participants reported 5 treatment-emergent adverse events (TEAEs), with mild and moderate severity.

Unbound zilucoplan in plasma was only detected 4 hours post-dose. In UP0094 study report, a mean plasma concentration of unbound zilucoplan in moderate hepatic impairment (HI) is reported as 16.79 ng/mL, while in the corresponding bioanalysis report in table 4, the highest concentration in this whole study was 13.3 ng/mL in plasma:PBS 1:1. The reported geometric mean (CV%) of the unbound zilucoplan fraction was 0.38% (59) in the moderate HI liver function study participants. The mean unbound zilucoplan concentrations or fractions were not calculated in the normal liver function study participants because 3/8 subjects had concentrations below lower limit of quantitation. The median percent of unbound zilucoplan fraction (fu%) in the Normal arm was 0.37% (range:0.27 - 0.51 %).

Zilucoplan $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were both 24% lower in subjects with moderate HI liver function compared with study participants with normal liver function. Zilucoplan C_{max} was similar between groups. Moderate HI study participants had a 32% higher CL/F and ~36% higher Vz/F normalised to body weight (i.e., 0.11 L/kg in moderate HI study participants and 0.082 L/kg in study participants with normal liver function). As a consequence, the $t_{1/2}$ remained similar (150 h vs. 162 h) between the 2 arms indicating that despite moderate hepatic impairment, the metabolic function of the liver did not impact PK of total zilucoplan.

For the 2 metabolites, systemic exposure based on $AUC_{0\text{-last}}$ and peak exposure based on C_{max} were higher in study participants with moderate HI liver function compared with study participants with normal liver function.

Despite the decrease zilucoplan AUC, the PD analyses did not identify any meaningful differences in either total C5 plasma levels nor inhibition of sheep RBC (sRBC) lysis between moderate HI and normal study participants. The applicant considers that a zilucoplan dose adjustment in participants with moderately impaired liver function is not warranted.

The faecal samples were not weighed, and therefore the total amounts of zilucoplan and metabolites in faeces could not be assessed. Based on the concentrations of zilucoplan and metabolites in faeces and the estimated fraction excreted by the faecal route, zilucoplan was minimally excreted in both the normal and in the moderate HI study participants (<1% of dose in total).

Gender

In the Phase 3 study (MG0010), approximately 60% of the participating patients were female and 40% were male. Sex was not a statistically significant covariate in the popPK analysis.

Race

A single- and multiple-dose PK study was performed in Japanese and Caucasian subjects (UP0113). The subjects were given a single injection of 0.1 or 0.3 mg/kg or once daily injections of 0.3 mg/kg of zilucoplan for 14 days. There were no greater differences in the PK of zilucoplan between Japanese as compared to Caucasian subjects. In addition, race was not identified as a statistically significant covariate in the popPK analysis.

The PK of the metabolites were also investigated. At a dose of 0.3 mg/kg the following were observed:

There were trends towards higher AUC and/or C_{max} of RA102758 in Japanese as compared to Caucasian subjects, but the CIs were wide or included 100%. However, the AUC_T was not determined in most of the subjects in the multiple-dose cohort. Following repeated injections for 14 days, there were no greater differences in pre-dose plasma concentrations of RA102758 between the races.

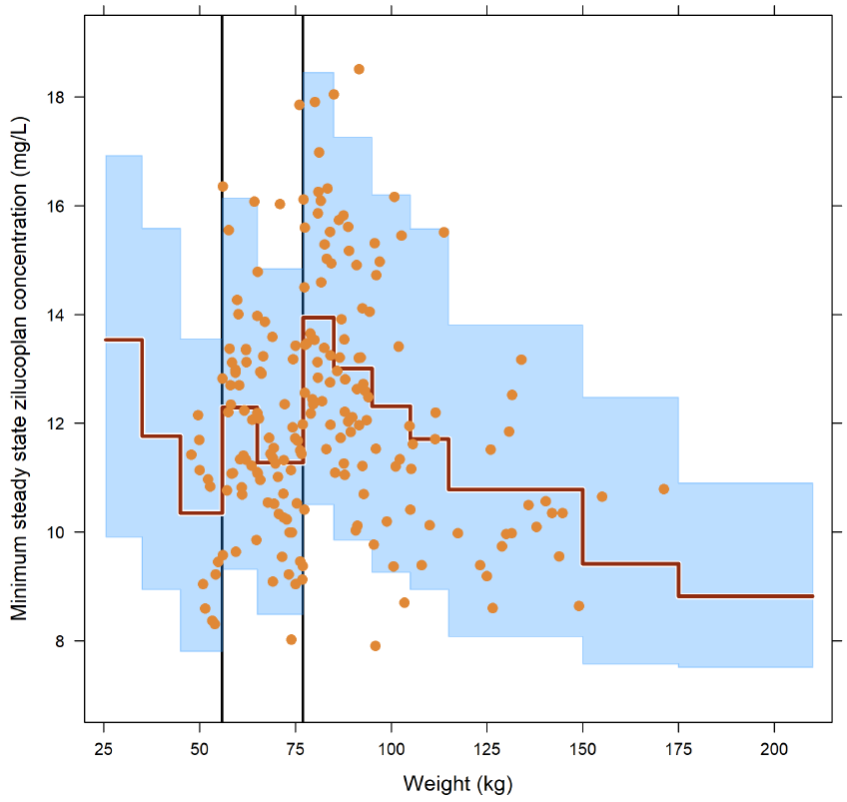
There were trends towards lower AUC and/or C_{max} of RA103488 in Japanese as compared to Caucasian subjects, but after repeated injections (day 14) the CI included 100% (indicating no difference in exposure). However, the AUC_T was not determined in most of the subjects in the MD cohort. Following repeated injections for 14 days, the pre-dose concentrations of RA103488 tended to be lower in Japanese as compared to Caucasian subjects.

The effect on sRBC haemolysis or total C5 plasma levels, expressed as percent change from baseline (CBL), appeared to be relatively similar between Japanese and Caucasian participants.

Body weight

In the Phase 3 study (MG0010), the body weight range among patients receiving zilucoplan was 49.6 to 145 kg. In the clinical studies, Zilucoplan was dosed by body weight, and body weight was also included as a covariate (*a priori*) in the popPK model, with estimated exponents. In a simulation analysis, the effect of the three dose categories on exposure measures was investigated as a function of body weight. The results for trough concentration at steady state are provided in Figure 7. These results suggest that the intended dosing schedule results in adequate correction of the impact of body weight on exposure to zilucoplan.

Figure 7: Distribution of trough steady state zilucoplan concentration by weight using the final population PK model



Red line and blue area: median and 90% of simulated values for patients sampled from the NHANES DXA database. Orange circles: individual predicted values for gMG patients in MG0010, vertical black lines: weights (56 and 77 kg) where dose changes from 16.6 mg to 23 mg to 32.4 mg

Age

In the Phase 3 study (MG0010), the age range among patients receiving zilucoplan was 20 to 75 years. Age was not a statistically significant covariate in the popPK analysis.

Pharmacokinetic interaction studies

No *in vivo* drug-drug interaction (DDI) study has been performed.

Pharmacokinetics using human biomaterials

In vitro studies were performed to investigate the DDI potential of zilucoplan and RA102758.

Effect of other medicines on zilucoplan and RA102758

Zilucoplan is a peptide that is expected to be degraded into small peptides and amino acids via catabolic pathways. CYP4F2 contributes to a minor part of the metabolism.

Zilucoplan seems not to be a substrate of P-gp, BCRP, MRP2, MRP3, OATP1B1 and OATP1B3. There are some unclarities regarding the recovery in the BCRP and P-gp experiments, for which reason the results should be interpreted with caution. RA102758 is not a substrate of OATP1B1/B3.

Effect of zilucoplan and RA102758 on other medicines

Zilucoplan and RA102758 seem not to be a direct or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A and CYP4F (only direct inhibition was studied) at clinically relevant concentrations.

Zilucoplan does not inhibit the UGT enzymes, UGT 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15. In addition, zilucoplan seems not to induce CYP1A2, CYP2B6 and CYP3A4.

Inhibition of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, BSEP and NTCP (only investigated for zilucoplan) seems unlikely *in vivo*. RA102758 does not inhibit OATP1B1/B3 at clinically relevant concentrations, whereas Zilucoplan inhibited OATP1B1 and OATP1B3 with IC_{50} values of 2.4 and 2.1 µM, respectively. These values are close to the systemic DDI cut-off (1.7 µM). Zilucoplan seems not to be a clinically relevant inhibitor of MRP2. However, it cannot be excluded that zilucoplan inhibits MRP3 *in vivo*.

Exposure relevant for safety evaluation

Following repeated SC injections of 0.3 mg/kg/day, the geometric mean C_{max} and AUC_{0-24} of ZLP at steady state were 12300 ng/mL and 259000 ng*h/mL, respectively (UP0113). The corresponding C_{max} and AUC_{0-24} of RA102758 were 1270 ng/mL and 287100 ng*h/mL, respectively.

2.6.2.2. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

Thorough QT study (UP0093)

The thorough QT study UP0093 investigated the effects of 7 daily doses of zilucoplan 0.6 mg/kg SC on cardiac repolarisation. Sensitivity was demonstrated with moxifloxacin as an active control.

The geometric mean systemic exposure of total zilucoplan was higher on Day 7 compared with Day 1 for both C_{max} (D1: 8372 and D7: 23940 ng/mL) and AUC_T (D1: 149000 and D7: 459100 h*ng/mL), indicating accumulation as a result of daily dosing and reflecting the relatively slow clearance of zilucoplan. Compared with Day 1, the C_{max} and AUC_T on Day 7 had increased by a factor of approximately 3. The peak concentration was achieved at 4 hours post-dose after single and repeated dosing. The variability between the participants remained comparable between Day 1 and Day 7. The t_{max} remained constant between single and multiple dosing at 4 hours post-dose.

The systemic exposure of RA102758 was higher on Day 7 compared with Day 1 for both C_{max} (D1: 119 and D7: 1680 ng/mL) and AUC_T (D1: 1270 and D7: 35700 h*ng/mL). Compared with Day 1, the C_{max} and AUC_T on Day 7 had increased by factors of approximately 28 and 14, respectively. The t_{max} remained constant between single and multiple dosing at 24 hours post dose.

The systemic exposure of RA103488 was higher on Day 7 compared with Day 1 for both C_{max} (D1: 174 and D7: 1610 ng/mL) and AUC_{tau} (D1: 2070 and D7: 34000 h*ng/mL). Compared with Day 1, the C_{max} and AUC_T on Day 7 had increased by factors of approximately 9 and 17, respectively. The t_{max} was higher for the single dose compared with multiple dosing.

No trends were visible in the hysteresis analysis of ΔQTcF (QT corrected using the Fridericia method) under zilucoplan and under placebo (ΔΔQTcF) for any of zilucoplan or its metabolites.

In the by-time point analysis, mean ΔΔHR was below 10 bpm for the zilucoplan group across all post dose time points, thereby demonstrating that ZLP has no relevant effect on heart rate.

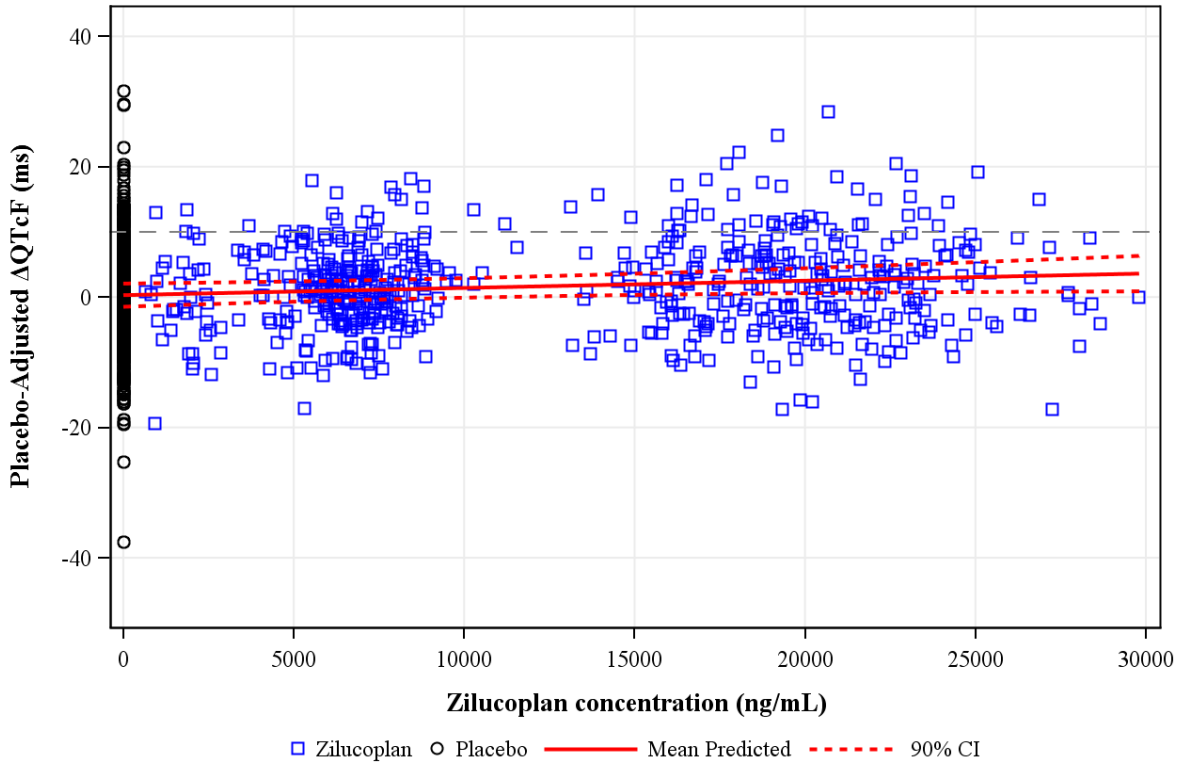
The relationship between plasma concentrations of zilucoplan and its metabolites RA102758 and RA103488 and ΔQTcF was quantified using a linear mixed-effects modeling approach. In total, 7 concentration-QTc (C-QTc) models were evaluated: the full model with zilucoplan, RA102758, and RA103488 (Model A), a model with zilucoplan and RA102758 (Model B), a model with zilucoplan and RA103488 (Model C), a model with RA102758 and RA103488 (Model D), a model with zilucoplan alone

(Model E), a model with RA102758 alone (Model F), and a model with RA103488 alone (Model G). The model selection was based on the Akaike Information Criterion (AIC) and the t-value for the treatment effect-specific intercept estimator. A significant treatment effect-specific intercept is not biologically plausible and may indicate hysteresis or model misspecification.

The treatment effect-specific intercepts for the Models A through G were not statistically significant (absolute t-value<1.95). The model with zilucoplan alone (Model E) was chosen as the primary model, since it had the smallest AIC value among Models A through G.

The relationship between the individually observed plasma concentrations of zilucoplan and estimated ΔΔQTcF for Model E (ZLP alone) are shown in Figure 8.

Figure 8: Scatter plot of observed plasma concentrations (zilucoplan alone) and estimated ΔΔQTcF for Model E (PK/QTc Analysis Set; UP0093)



The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which was calculated from the equation ΔΔQTcF(ms)=0.29(ms)+0.00011(ms per ng/mL)×zilucoplan plasma concentration (ng/mL). The plotted points denote the pairs of observed drug plasma concentrations and estimated ΔΔQTcF by study participants for each active group and placebo group. The individually estimated $\Delta\Delta QTcF_{i,k}$ equals the individual $\Delta QTcF_{i,k}$ for study participant i administered with active drug or placebo at time point k minus the estimation of the time effect at time point k

The estimated population slope of the C-QTc relationship was 0.00011 ms per ng/mL (90% CI: 0.000001 to 0.000220; p=0.0961) for ZLP with a small, not statistically significant treatment effect specific intercept of 0.29 ms (90% CI: −1.485, 2.069; p=0.7858). At the geometric mean C_{max} of zilucoplan on Day 1 (8372 ng/mL) and Day 7 (23940 ng/mL), the effect on ΔΔQTcF can be predicted to 1.2 ms (90% CI: −0.28 to 2.71) and 2.9 ms (90% CI: 0.73 to 5.10), respectively. Based on this C-QTc analysis, a QTcF effect (ΔΔQTcF) exceeding 10 ms can be excluded within the observed range of ZLP plasma concentrations. It should be noted that the prediction results from all models (A-G) were similar and that all concluded that a QTc effect exceeding 10 ms can be excluded within the observed plasma concentration ranges of zilucoplan, RA102758, and RA103488.

Zilucoplan had no clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals, within the observed plasma concentration ranges.

Relationship between plasma concentration and effect

Exposure-response models were developed for Myasthenia Gravis Activities of Daily Living (MG-ADL) score and quantitative myasthenia gravis (QMG) score, respectively. The models were fitted to data from the Phase 2 study (MG0009) and the Phase 3 study (MG0010), where most data were from placebo or the 0.3 mg/kg dose level (only about 6% of the data were on the 0.1 mg/kg dose level). Due to the limited nature of the data, and the limited importance of the models, these analyses are not further described.

2.6.3. Discussion on clinical pharmacology

MG is characterised by the production of autoantibodies targeting proteins that are critical for the normal transmission of neurotransmitter signals from nerves to muscles. This activates the classical complement pathway including cleavage of complement C5 into C5a and C5b and deposition of the cytolytic MAC (C5b-9) on the post-synaptic membrane of the NMJ.

Zilucoplan is a 15-amino acid peptide that binds to C5 with high affinity and prevents its cleavage into C5a and C5b. Inhibition of C5 cleavage prevents the downstream activity of the MAC. Zilucoplan binds to the portion of C5 that corresponds to C5b. In binding to this region of C5, should any C5b be formed, it will be blocked from binding to C6 by ZLP, which further prevents the subsequent assembly of the MAC (C5b-9).

Pharmacokinetics

The applicant has performed several clinical pharmacology studies to describe the ADME characteristics of zilucoplan and to identify special populations or DDI with risk for altered exposure. The PK was also thoroughly investigated for the major metabolite, RA102758, and the active metabolite RA103488.

Referring to a per kilogram dose can be misleading for the prescriber, when the actual doses administered during clinical trials were flat doses within body weight bands. For clarity, the applicant changed from '0.3 mg/kg' to 'recommended dose' throughout the SmPC as requested.

Methods

Quantification of zilucoplan, RA102758 and RA103488

Overall, the bioanalytical methods (LC-MS/MS) for analysis of ZLP, RA102758 and RA103488 in plasma and urine were adequately validated for their intended purpose, despite the lack of cross-validation between the two methods used for analysis of total concentrations of zilucoplan in plasma (methods 1 and 2). Method 1 was only used in the first study in humans, which included only a limited number of subjects (in total 18 subjects were dosed with ZLP), and therefore this issue was not further pursued.

The LC-MS/MS method that was used to determine ZLP, RA102758, and RA103488 in human faeces (study UP0094) has not been assessed since there were limitations in the collection of the faeces samples.

The bioanalytical report for analysis of plasma concentrations of ZLP, RA102758 and RA103488 in the ongoing study, MG0011, was provided. The report included data up to and including 14 October 2022. The performance of the method seemed adequate. However, it was noted that multiple samples were analysed outside of the validated stability period of 367 days at -80°C. The clinical study is currently ongoing and the long-term stability in human plasma will be assessed after a period of ≥696 days to

extend the current stability period. The applicant has committed to provide final bioanalytical report, including long term stability, when the clinical study is completed.

Immunogenicity

All three ADA methods were fully validated, and cut-off points were determined in healthy subjects using state of the art procedures.

The initial method has adequate drug tolerance to be used for the analysis of samples from study UP0112. However, due to the poor drug tolerance using the second-generation assay, immunogenicity data from study MG0009 should be considered inconclusive. The drug and target tolerance of the third generation ADA method is sufficient for use in the phase 3 studies. No target interference is expected with total C5 levels.

The CHMP recommended that a bioanalytical report including immunogenicity data from study MG0011 is submitted once it is completed. The APA assay has insufficient sensitivity and drug tolerance at 100 ng/mL APAs, with a sensitivity of 200 ng/mL in the screening and 134 ng/mL in the confirmatory assay. The difference in sensitivity in the two tiers entails that some samples that could potentially be confirmed positive would not be tested as they would be screened negative. The applicant considers it unlikely that a significant number of additional positive sampled would be detected if the sensitivity of the screening and confirmatory assay were similar. Additionally, since there was no association of positive APA status with efficacy or safety, there would be no clinical relevance of these additional samples. This is agreed.

Regarding the NAb, the applicant's view that the assays are unsuitable is agreed, since significant interferences would be expected. Given the low incidence of ADAs, and current data indicating no impact on safety and efficacy, the absence of a reliable NAb assay is acceptable.

The bioanalytical reports from study samples indicate the within study validation was adequate.

Population PK

The developed popPK model is used to describe the nonlinear PK of zilucoplan and it is used to support equal exposure across body weight, with the suggested weight bracketed doses. A thorough evaluation of the model has been conducted by the applicant, showing that the model appropriately describes data across dose, body weight, single and multiple dose, and population (HV/gMG patient).

Absorption, distribution, metabolism and elimination

In general, the PK of zilucoplan and its metabolites, RA102758 and RA103488, have been sufficiently described.

No bioequivalence study has been performed. The to-be-marketed formulation (process 2.2) has not been tested clinically. Since the issues raised in the quality section are adequately solved, it is agreed that no clinical bioequivalence study is needed.

The AUC of zilucoplan increased less than proportional with an increase in dose. There seems to be a faster elimination after repeated as compared to single administration, indicating that the PK is likely driven by binding to the target, i.e. once the target is saturated, elimination increases. This is also supported by the popPK analyses. No time-dependency was observed.

As a peptide, ZLP is expected to be degraded into small peptides and amino acids via catabolic pathways.

In human hepatocytes, RA102758 and M2169/1, were the metabolites that accounted for the largest part of the total radioactivity (16900). The applicant clarified that M2169/1 is a minor circulating metabolite in humans. RA102758 and RA103488 were the two largest metabolites identified in human plasma. RA102758 is inactive, whereas RA103488 is a pharmacologically active metabolite with a similar potency as parent compound *in vitro* (see non-clinical sections). RA102758 is considered to be a major

metabolite, as its AUC (expressed in molar units) is approximately 25% of the parent AUC. RA103488, is mainly formed by CYP4F2, which only contributes to a minor part of the metabolism.

No human mass-balance study has been performed, this is acceptable considering the molecular structure of this peptide and that catabolic pathways are involved in the degradation of the compound. Based on unlabelled zilucoplan, it appears that excretion of zilucoplan, RA103488, and RA102758 into urine and faeces is minimal. However, the sampling was relatively short, compared to zilucoplan and its metabolites' half-lives. In addition, there were some problems with the faecal samples. Nevertheless, the provided analysis gives some indication that faecal excretion of zilucoplan and its metabolites is not a major route of elimination. Overall, it can be concluded that the excretion pathways have been sufficiently characterised.

Immunogenicity

The incidence of treatment-emergent ADA was low in the Phase III study (study MG0010) and remained low in the ongoing long-term efficacy and safety study, MG0011. No impact on the PK of zilucoplan was seen for ADAs and APAs. However, study MG0010 and MG0011 results indicate a higher incidence of treatment emergent APAs compared to ADAs, due to differences in sensitivity between the ADA and APA method. The ADA screening and confirmatory assays could only detect the APA positive control at higher concentrations (801 and 611 ng/mL, respectively), compared to a sensitivity in the 100 ng/mL range in the APA assay. This explains why the incidence of APAs is higher. Immunogenicity against PEG is in line with literature data.

The applicant provided summary tables with the ADA and APA status, presented by arm (placebo/ZLP vs ZLP/ZLP). Most patients were negative throughout for both ADA and APAs, 63% in the placebo arm and 59% in the ZLP arm. Consistent with the difference in sensitivity for APAs, the incidence of APA positive while ADA negative was 16% in both arms. Only 2 patients per arm (2.4%) were treatment induced ADA and APA positive, and additional 2 per arm were ADA positive but APA negative. Upon request, information on immunogenicity has been adequately moved to section 5.1 of the SmPC and updated to reflect Table 5.

Special populations

A dedicated renal impairment study showed that the exposure of zilucoplan decreases in severe renal impairment subjects, compared to subjects with normal renal function. The exposure of the metabolite RA103488 increased when renal function decreased, while the exposure of RA102758 was more variable. Overall, it is agreed that there is no need for dose adjustment for patients with renal impairment, as the difference compared to normal renal function is small. The SmPC text has been revised and is acceptable.

A dedicated hepatic impairment study indicated a statistically significant decrease in ZLP in moderate hepatically impaired subjects, with the consequence of a small increase of its metabolites RA102758 and RA103488). The discrepancy between two tables was clarified as caused by the dilution factor. The fu in the two arms seems overlapping, thus it could be acceptable to focus the analysis on total concentration. The applicant argues that despite an AUC decreased by 24% in moderate HI patients, the $C_{ss,ave}$ remains higher than the EC95 value of 4.45 mg/L, with no impact on the sRBC lysis. A 24% decrease of the trough concentration, compared to the geometric mean trough concentration observed at week 12 in the 0.3 mg/kg dose group in MG0009, would correspond to a trough concentration of 7.68 mg/L. This concentration is above both the predicted EC95 value, and the geometric mean trough concentration observed in the 0.1 mg/kg dose group in study MG0009 (5.14 mg/L). Based on the totality of data, it is agreed that there is no need for a dose adjustment for moderate HI patients. The proposed actionable recommendation for patients with severe HI in SmPC section 4.2 is acceptable.

There was no effect of age, race and gender on the PK of zilucoplan. There were no major differences in the systemic exposure of RA102758 between the races. However, the pre-dose plasma concentrations

of RA103488 (active metabolite) tended to be lower in Japanese as compared to Caucasian subjects. This is not considered clinically relevant since the plasma concentrations of this metabolite are much lower than parent. Thus, no dose-adjustments are needed based on age, race or gender. The information in the SmPC is generally supported.

In the clinical studies, Zilucoplan was dosed by body weight, and body weight was also included as a covariate (*a priori*) in the popPK model (with estimated coefficients). Based on simulations, the proposed weight bracketed doses appear to result in comparable median exposure across body weight for subjects weighing 25 to 150 kg, while subjects weighing ≥150 kg have a lower simulated median exposure. The applicant argues that the simulated median trough concentration for subjects with a body weight of 200 kg, receiving 32.4 mg QD, is just below 9 mg/L (10^{th} percentile just below 7 mg/L). This concentration is well above both the predicted EC95 value of 4.45 mg/L, and the geometric mean trough concentration observed in the 0.1 mg/kg dose group in study MG0009 (5.14 mg/L). Based on the totality of data, it is hence agreed that a higher dose of ZLP in patients ≥150 kg is not needed.

Interactions

The DDIs for zilucoplan and its major metabolite, RA102758, have been thoroughly investigated. No clinical DDI study has been performed. For victim DDIs, this is acceptable considering that zilucoplan is a peptide that is expected to be degraded into small peptides and amino acids via catabolic pathways and CYP4F2 contributes only to a minor part of the metabolism.

Zilucoplan and RA102758 as victim

Zilucoplan is not a substrate of MRP2, MRP3, OATP1B1 and OATP1B3. ZLP seems not to be a substrate for P-gp and BCRP. However, there are unclarities regarding the recovery in the P-gp and BCRP assays. Considering that ZLP is administered SC and that there appears to be a small amount excreted into faeces, this is not further pursued. The involvement of renal transporters was not investigated, which is acceptable since renal excretion of ZLP appears to be minimal. RA102758 is not a substrate of OATP1B1/B3.

Zilucoplan and RA102758 as perpetrator

Inhibition of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, BSEP and NTCP seems unlikely *in vivo*. ZLP inhibited OATP1B1 and OATP1B3 with IC50 values of 2.4 and 2.1 µM, respectively. These IC_{50} values are close to the systemic cut-off (1.7 µM). The applicant provided information supporting that the experiment is conducted under linear conditions. Thus, a clinically relevant inhibition of OATP1B1 and OATP1B3 *in vivo* seems unlikely. Inhibition of MRP2 and MRP3 cannot be excluded. The applicant discussed the clinical relevance of these interactions. It is agreed that the IC_{50} for MRP2 is slightly above the systemic DDI cut-off and therefore inhibition of MRP2 can be excluded *in vivo*. For MRP3 it is agreed that substrate specificity overlaps with other transporters and that there are currently no examples of sensitive MRP3 substrates, it is nevertheless a signal. Thus, SmPC section 5.2 includes a warning specifying that the clinical relevance is unknown. RA102758 does not seem to inhibit transporters known to be involved in clinically relevant *in vivo* drug interactions.

In vitro data indicate that inhibition of the major CYP enzymes, including CYP4F, is unlikely *in vivo*. Zilucoplan does not seem inhibit the UGT enzymes (UGT 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15) or induce CYP1A2, CYP2B6 and CYP3A4 at clinically relevant concentrations. However, several of the induction experiments indicated down-regulation of the mRNA, including the negative control. For both CYP2B6 and CYP3A4, a similar decrease in mRNA levels was observed in the negative control (flumazenil) as in the incubations with zilucoplan, and therefore down-regulation of the mRNA can be ruled out. For CYP1A2, since no concentration-dependent decrease in mRNA levels was evident, down-regulation of the mRNA seems unlikely, as suggested by the applicant. This issue is not further pursued.

Primary pharmacology

The primary PD of zilucoplan were studied throughout the clinical development programme using the sRBC lysis assay and determination of total C5 plasma levels. These PD markers are relevant to characterise the mode of action of Zilucoplan which is the inhibition of complement activation. Similar assays have been used to characterise the primary PD of C5-related products. However, it should be noted that, unlike these products, only total C5 plasma levels were determined in the zilucoplan clinical programme and not serum free C5 levels. A rapid and sustained reduction of cell lysis was seen after ZLP treatment. This effect was somewhat more pronounced and faster with the 0.3mg/kg dose than with the 0.1mg/kg dose.

Secondary pharmacology

With an administration of 7 days of 0.6 mg/kg ZLP, ZLP and its metabolites seemed to reach steady state in study UP0093. The exposure following 0.6 mg/kg ZLP was supratherapeutic with regards to $C_{max.}$ The elimination was increased upon multiple doses of 0.6 mg/kg, compared to 0.3 mg/kg, showing some less than dose proportional increase in AUC. The exposure was however still higher than the therapeutic exposure from Phase III studies.

Given the relatively flat concentration-time profile of ZLP and its metabolites, no trends could be identified in the hysteresis analysis.

The study demonstrated sufficient sensitivity with moxifloxacin.

The applicant's conclusion that there was no meaningful effect of ZLP on cardiac function is agreed.

2.6.4. Conclusions on clinical pharmacology

The PK of zilucoplan and its major metabolite, RA102758, has been well described. No major concern has been identified. The risk of DDIs is low. The SmPC is acceptable.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Submission of final immunogenicity data and bioanalytical reports for study MG0011 for ADA and APA.
- Submission of final bioanalytical report for zilucoplan, RA102758 and RA103488, including long term stability, for study MG0011.

2.6.5. Clinical efficacy

Efficacy was studied in one phase II dose-finding study (MG0009) and two phase III studies, one blinded and controlled (MG0010) and one open label (MG0011). Characteristics of these studies are presented in the table below.

Table 7: Clinical efficacy studies

Study ID[a] Countries Study Status	Study Design	Study period	Number of study participants receiving:		Maximum duration of treatment
			ZLP	Placebo	
Primary efficacy study					
MG0010 RAISE (RA101495-02.301) Canada, France, Germany, Italy, Japan, Norway, Poland, Spain, United Kingdom, United States Complete	Phase 3, MC, R, DB, PC	Treatment Period	0.3mg/kg SC once daily: 86	88	12 weeks
Supporting efficacy study					
MG0009 (RA101495-02.201) Canada, United States Complete	Phase 2, MC, R, DB, PC	Main Portion	0.1mg/kg SC once daily: 15 0.3mg/kg SC once daily: 14	15	12 weeks
		Extension Portion	0.1mg/kg SC once daily: 22[b] 0.3mg/kg SC once daily: 41	NA	Approximately 4 years (as of the clinical cut-off date)
Long-term study					
MG0011 RAISE-XT (RA101495-02.302) Canada, France, Germany, Italy, Japan, Norway, Poland, Spain, United Kingdom, United States Ongoing	Phase 3, MC, OLE for MG0009 and MG0010	Treatment Period	0.3 mg/kg SC once daily: 199	NA	3.9 years[c]

a) The first and second study numbers are the UCB and Ra Pharmaceuticals, Inc. (a member of the UCB group of companies) study numbers, respectively, and the study is referred to by the UCB study number throughout the document.

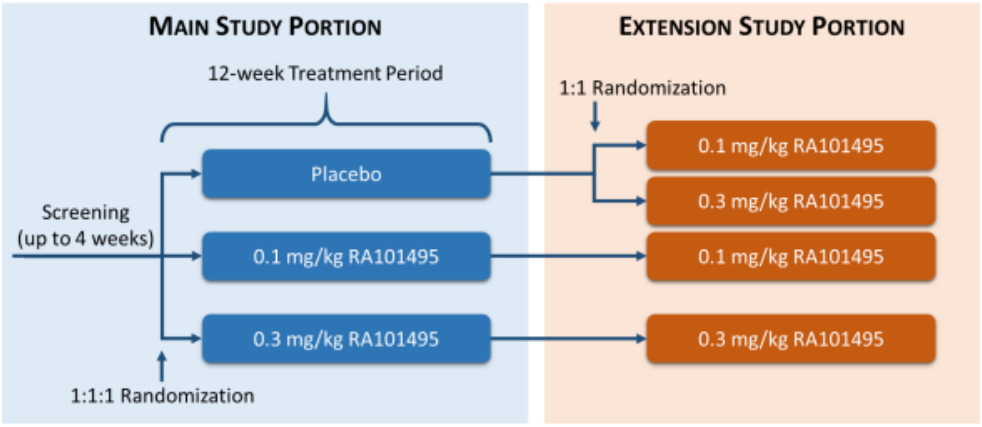
b) Following implementation of Protocol Amendment 3.0, and upon appropriate reconsent, all study participants ongoing in the Extension Portion received the ZLP 0.3mg/kg dose that had been selected for MG0010 and were eventually enrolled (at variable times relative to the Baseline of MG0009) in the open-label extension study, MG0011 (RAISE-XT).

c) Maximum duration of treatment from start of the open-label extension at the time of interim data cut, 18 Feb 2022.

2.6.5.1. Dose response study

MG0009 was a Phase 2, multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of ZLP 0.1mg/kg/day and 0.3mg/kg/day doses in study participants with gMG.

Figure 9: Schematic diagram of Study MG0009



Note ZLP was named RA101495 previously in the development process
Note Following protocol version 3.0, all study participants received ZLP 0.3mg/kg/day during the extension portion.

Inclusion and exclusion criteria were similar to those in the main study MG0010.

Sample size, randomisation, blinding/masking

Subjects who met all entry criteria were to be randomised in a 1:1:1 ratio to receive daily SC doses of 0.1 mg/kg ZLP, 0.3 mg/kg ZLP, or matching placebo. At randomisation subjects were stratified based on baseline QMG Score (≤ 17 versus ≥ 18).

This was a double-blind study. Study drug was to be provided in prefilled syringes for self-injection using weight bracketed dosing. Subjects and study staff were to remain blinded to treatment assignments during the extension portion until after the data from the main portion of the study had been cleaned, locked, and unblinded. Unblinding of treatment assignment prior to initiation of rescue therapy was not allowed, unless critical for reasons of subject safety.

The planned enrolment was approximately 36 study participants. With 12 subjects per treatment group, the study had a power of 81% to detect a difference of 4.5 between one of the active dose arms and placebo in CBL to Week 12 (Day 84) in QMG score based on a 1-sided type I error of 0.10 and assuming a standard deviation of 5.0.

Subjects who prematurely discontinued participation in the study could be replaced in order to obtain at least 12 evaluable subjects per treatment arm.

All subjects who completed the Day 84 visit had the option to continue treatment in an extension period. Subjects initially assigned to active treatment during the main study period were to continue the same dose of study drug. Subjects initially randomised to the placebo arm were randomised in a 1:1 ratio to 0.1 mg/kg ZLP or 0.3 mg/kg ZLP. This randomisation was to occur at the screening visit when a subject was initially randomised to the double-blind main study period.

Statistical methods

The primary analysis of the study was to be performed when all subjects had completed the main portion.

The primary analysis population was the modified intention-to treat (mITT) including all subjects in the intention-to-treat (ITT) Population (all randomised) who had received at least 1 dose of study drug.

For the primary efficacy endpoint, the CBL to Week 12 (Day 84) in QMG score, treatment group differences were to be assessed by an analysis of covariance (ANCOVA) model, with treatment as a factor and baseline QMG score as a covariate.

The primary efficacy analysis was the comparison of the 0.3 mg/kg dose group versus the placebo dose group based on the ANCOVA model at a 1-sided 0.10 significance level.

The comparison of the 0.1 mg/kg dose group versus the placebo dose group was considered a secondary efficacy endpoint analysis tested at the 1-sided 0.10 level.

In addition, a test of linear trend across the 3 treatment groups was planned as was a test for treatment effect pooling the 0.1mg/kg and 0.3mg/kg dose groups versus placebo.

The secondary efficacy endpoints: Week 12 CBL in MG-ADL, Myasthenia Gravis-Quality of Life 15-item scale revised (MG-QOL15r), and MG Composite (MGC) were to be analysed by an ANCOVA model similar to the primary efficacy endpoint analysis. For the 'Subjects with ≥ 3-point reduction in QMG score at Week 12' and 'Subjects requiring rescue therapy over the 12-week Treatment Period' secondary efficacy endpoints, the rate of subjects meeting the endpoint for each of the active treatment groups were to be compared with the placebo group using a Fisher's exact test at the 1-sided 0.10 level.

The primary method for handling missing data was last-observation-carried-forward (LOCF). For the LOCF algorithm, if a study participant was missing a value, the closest non missing endpoint value prior to the missing value was imputed for the missing value. This included the baseline value and values from unscheduled visits.

Additionally, if a subject received rescue therapy, efficacy endpoints that occurred after rescue therapy were censored and imputed using LOCF and the closest non-missing endpoint value prior to the initiation of rescue therapy.

There were no adjustments to the type I error rate for the multiple secondary efficacy analyses.

Results

First study participant enrolled was 28 Nov 2017 and last study participant completed the study 19 Nov 2020. A total of 22 Investigators enrolled study participants at 29 sites, 26 sites in the United States and 3 sites in Europe.

Table 8: Disposition and discontinuation reasons – main portion (ITT Population) MG0009

Category	**Placebo N=15 n (%)**	**ZLP 0.1mg/kg/day N=15 n (%)**	**ZLP 0.3mg/kg/day N=15 n (%)**	**Total N=45 n (%)**
Completed Main Portion[a]	15 (100)	15 (100)	13 (86.7)	43 (95.6)
Discontinued Main Portion	0	0	2 (13.3)	2 (4.4)
Primary reason for discontinuation				
Lost to follow up	0	0	1 (6.7)	1 (2.2)
Other	0	0	1 (6.7)	1 (2.2)
Enrolled in the Extension Portion	14 (93.3)	15 (100)	13 (86.7)	42 (93.3)

Table 9: Demographic characteristics – overall (ITT Population) MG0009

Characteristic	**Placebo N=15 n (%)**	**ZLP 0.1mg/kg/day N=15 n (%)**	**ZLP 0.3mg/kg/day N=15 n (%)**	**Total N=45 n (%)**
Sex, n (%)				
Female	11 (73.3)	8 (53.3)	5 (33.3)	24 (53.3)
Male	4 (26.7)	7 (46.7)	10 (66.7)	21 (46.7)
Age (years)				
N	15	15	15	45
Mean (SD)	48.4 (15.7)	45.5 (15.6)	54.5 (14.9)	49.5 (15.5)
Median	43.0	52.0	58.0	54.0
Min, max	23, 73	20, 65	21, 76	20, 76
Age Group, n (%)				
<65 years	13 (86.7)	14 (93.3)	11 (73.3)	38 (84.4)
≥65 years to <75 years	2 (13.3)	1 (6.7)	3 (20.0)	6 (13.3)
≥75 years	0	0	1 (6.7)	1 (2.2)
Weight (kg)				
N	15	15	14	44
Mean (SD)	85.27 (21.44)	93.71 (24.72)	110.94 (30.79)	96.31 (27.38)
Median	79.10	87.50	99.70	91.15
Min, max	56.4, 128.3	58.0, 140.3	75.0, 171.1	56.4, 171.1
Min, max	21.46, 46.01	24.14, 43.79	25.06, 55.87	21.46, 55.87

Table 10: Baseline disease characteristics (mITT Population) MG0009

Characteristic	**Placebo N=15 n (%)**	**ZLP 0.1mg/kg/day N=15 n (%)**	**ZLP 0.3mg/kg/day N=14 n (%)**	**Total N=44 n (%)**
MGFA Class at Screening	15	15	14	44
Class II	7 (46.7)	5 (33.3)	5 (35.7)	17 (38.6)
Class III	8 (53.3)	10 (66.7)	5 (35.7)	23 (52.3)
Class IV	0	0	4 (28.6)	4 (9.1)
Age at Disease Onset (years), n	15	15	14	44
Mean (SD)	40.3 (17.8)	37.3 (16.0)	46.9 (19.5)	41.4 (17.8)
Median	31.0	29.0	53.5	42.5
Min, max	15, 64	17, 63	15, 69	15, 69
Baseline QMG score, n (%)				
N	15	15	14	44
Mean (SD)	18.7 (4.0)	18.7 (4.0)	19.1 (5.1)	18.8 (4.3)
Median	17.0	18.0	18.5	18.0
Min, max	14, 30	13, 29	12, 33	12, 33
p-value	-	-	-	0.9447
Baseline QMG score, n (%)				
N	15	15	14	44
≤17	8 (53.3)	6 (40.0)	6 (42.9)	20 (45.5)
≥18	7 (46.7)	9 (60.0)	8 (57.1)	24 (54.5)
Baseline MG-ADL score				
N	15	15	14	44
Mean (SD)	8.8 (3.6)	6.9 (3.3)	7.6 (2.6)	7.8 (3.2)
Median	9.0	7.0	7.5	7.0
Min, max	3, 14	0, 11	2, 11	0, 14
p-value	-	-	-	0.2815

Outcomes and estimation

Main portion of study MG0009

The primary efficacy endpoint was the CBL to Week 12 QMG score. Prespecified significance testing was performed at a 1-sided alpha of 0.10.

Table 11: Change from baseline QMG score over time - main portion (mITT Population [LOCF Ancova]) MG0009

MMRM ANCOVA **Timepoint** Variable	**Placebo N=15**	**ZLP 0.1mg/kg/day N=15**	**ZLP 0.3mg/kg/day N=14**	**ZLP 0.1mg/kg/day + 0.3mg/kg/day N=29**
Week 12				
N	15	15	14	29
LS mean (SE) [a]	-3.2 (1.2)	-5.5 (1.2)	-6.0 (1.2)	-5.8 (0.9)
80% CI [a]	(-4.8, -1.6)	(-7.0, -3.9)	(-7.7, -4.4)	(-6.9, -4.6)
LS mean difference (SE) [b]	-	-2.3 (1.7)	-2.8 (1.7)	-2.6 (1.5)
80% CI [b]	-	(-4.5, -0.1)	(-5.1, -0.6)	(-4.4, -0.6)
1-sided p-value [b]	-	0.0941	0.0538	0.0444

The continuous secondary efficacy variables (CBL to Week 12 in MG-ADL, MG-QOL15r, and MGC) were analysed similar to the primary efficacy endpoint analysis; each of the active doses were compared with the placebo group at the 1-sided 0.10 significance level.

Table 12: Change from baseline MG-ADL score, MG-QOL15r score and MGC score over time - main portion (mITT Population [LOCF Ancova]) MG0009

Timepoint Variable	**Placebo N=15**	**ZLP 0.1mg/kg/day N=15**	**ZLP 0.3mg/kg/day N=14**	**ZLP 0.1mg/kg/day + 0.3mg/kg/day N=29**
Week 12 MG-ADL				
N	15	15	14	29
LS mean (SE) [a]	-1.1 (0.9)	-3.3 (0.9)	-3.4 (0.9)	-3.3 (0.6)
80% CI	(-2.2, 0.1)	(-4.4, -2.1)	(-4.6, -2.2)	(-4.2, -2.5)
LS mean difference (SE) [b]	-	-2.2 (1.3)	-2.3 (1.3)	-2.3 (1.1)
80% CI [b]	-	(-3.9, -0.5)	(-4.0, -0.6)	(-3.7, -0.8)
1-sided p-value [b]	-	0.0470	0.0392	0.0233
Week 12 MG-QOL15r				
N	15	15	14	29
LS mean (SE) [a]	-2.1 (1.7)	-7.4 (1.7)	-5.9 (1.7)	-6.6 (1.2)
80% CI	(-4.3, 0.1)	(-9.6, -5.2)	(-8.1, -3.6)	(-8.2, -5.1)
LS mean difference (SE) [b]	_	-5.3 (2.4)	-3.7 (2.4)	-4.5 (2.0)
80% CI [b]	_	(-8.4, -2.1)	(-6.9, -0.6)	(-7.2, -1.8)
1-sided p-value [b]	_	0.0170	0.0624	0.0169
Week 12 MGC				

N	15	15	14	29
LS mean (SE) [a]	-3.3 (1.6)	-5.3 (1.5)	-7.4 (1.6)	-6.3 (1.1)
80% CI	(-5.4, -1.3)	(-7.3, -3.3)	(-9.4, -5.3)	(-7.7, -4.9)
LS mean difference (SE) [b]	-	-2.0 (2.2)	-4.1 (2.2)	-3.0 (1.9)
80% CI [b]	-	(-4.9, 0.9)	(-7.0, -1.1)	(-5.5, -0.5)
1-sided p-value [b]	-	0.1866	0.0391	0.0660

a) LS means, standard errors, CIs, and p-values were from an ANCOVA model on the change from Baseline efficacy score with a fixed factor for treatment, and Baseline score as a covariate.

b) p-values (tested at the 1-sided 0.10 significance level), LS mean differences and associated confidence intervals were presented for each ZLP dose group (and combined group) compared with the placebo group.

Extension portion of study MG0009

In the Extension Portion of the study, study participants assigned to a ZLP dose group during the Main Portion of the study continued to receive the same dose of ZLP during the Extension Portion. Study participants assigned to the placebo arm during the Main Portion of the study were randomised in a 1:1 ratio to receive ZLP 0.1mg/kg/day or ZLP 0.3mg/kg/day. After a planned interim analysis and the implementation of Protocol Version 3, all study participants received the ZLP 0.3mg/kg/day dose for the remainder of the Extension Portion.

Change from baseline over time -24 weeks of active treatment.

Study participants were able to complete 24 weeks of active treatment in a combination of the Main Portion and first 12 weeks of the Extension Portion or during 24 weeks of the Extension Portion. This summary includes study participants in the active treatment dose group during the Main Portion, as well as study participants in the placebo arm during the Main Portion who switched to the active treatment dose group during the Extension Portion.

Table 13: Change from baseline QMG score over time - first 24 weeks of active treatment (ZLP Safety Population [LOCF]) MG0009

Timepoint Variable	**ZLP 0.1mg/kg/day N=22**		**ZLP 0.3mg/kg/day N=21**		**ZLP 0.1mg/kg/day + 0.3mg/kg/day N=43**	
	Value	**CFB**	**Value**	**CFB**	**Value**	**CFB**
Week 24						
n	22	22	20	20	42	42
Mean (SD)	11.41 (5.36)	-6.05 (5.31)	10.65 (5.42)	-7.50 (5.24)	11.05 (5.34)	-6.74 (5.26)
Median	11.00	-5.50	10.50	-6.50	11.00	-6.00
Min, max	1.0, 24.0	-14.0, 1.0	2.0, 23.0	-20.0, -1.0	1.0, 24.0	-20.0, 1.0

Table 14: Change from baseline in secondary endpoints MG-ADL, MG-QOL15r and MCG score over time - first 24 weeks of active treatment (ZLP Safety Population [LOCF]) MG0009

Timepoint Variable	**ZLP 0.1mg/kg/day N=22**		**ZLP 0.3mg/kg/day N=21**		**ZLP 0.1mg/kg/day + 0.3mg/kg/day N=43**	
	Value	**CFB**	**Value**	**CFB**	**Value**	**CFB**
Week 24 MG-ADL						
n	22	22	20	20	42	42
Mean (SD)	4.23 (3.29)	-2.68 (3.15)	4.00 (4.21)	-3.25 (3.46)	4.12 (3.71)	-2.95 (3.28)
Median	4.00	-2.00	2.00	-2.00	3.50	-2.00
Min, max	0.0, 11.0	-11.0, 3.0	0.0, 14.0	-10.0, 0.0	0.0, 14.0	-11.0, 3.0
Week 24 MG-QOL15r						
n	22	22	20	20	42	42
Mean (SD)	8.6 (7.9)	-8.5 (7.4)	9.2 (7.7)	-6.1 (7.5)	8.9 (7.7)	-7.4 (7.5)
Median	5.5	-8.5	8.0	-5.5	7.5	-8.0
Min, max	0, 27	-22, 2	0, 25	-26, 4	0, 27	-26, 4
Week 24 MGC						
n	22	22	20	20	42	42
Mean (SD)	8.0 (5.8)	-6.3 (6.7)	6.6 (5.9)	-7.6 (7.8)	7.3 (5.9)	-6.9 (7.2)
Median	7.0	-5.0	5.0	-7.5	6.0	-5.0
Min, max	0, 21	-22, 6	0, 21	-24, 5	0, 21	-24, 6

2.6.5.2. Main study

Study MG0010 A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Efficacy, Safety, and Tolerability of Zilucoplan in Subjects with Generalized Myasthenia Gravis

Protocol: RA101495-02.301 (RAISE) (UCB study MG0010)

Methods

This was a multicentre, randomised, double-blind, placebo-controlled study to confirm the efficacy, safety, and tolerability of 0.3 mg/kg zilucoplan in subjects with gMG. The study included a screening period of up to 4 weeks and a 12-week treatment period during which subjects were to return to the clinic at week 1, week 2, week 4, week 8, and week 12 to evaluate efficacy, safety, and tolerability.

- **Study Participants**

Inclusion criteria:

To be eligible for this study, study participants must have met all of the following inclusion criteria:

1. Male or female ≥18 years and <75 years

2. Able to provide informed consent, including signing and dating the informed consent form
3. Diagnosis of gMG [Myasthenia Gravis Foundation of America (MGFA) Disease Class II-IV] at Screening
4. Positive serology for AChR binding autoantibodies
5. MG-ADL score of ≥ 6 at Screening and Baseline
6. QMG score of ≥ 12 at Screening and Baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours)
7. Four or more of the QMG test items must have been scored at ≥ 2 at Screening and Baseline
8. No change in corticosteroid dose for at least 30 days prior to baseline or anticipated to occur during the 12-week Treatment Period
9. No change in IST, including dose, for at least 30 days prior to baseline or anticipated to occur during the 12-week Treatment Period
10. Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to the first dose of investigational medicinal product (IMP) at the Day 1 Visit. A booster vaccination should have also been administered as clinically indicated, according to the local standard of care, for study participants who had been previously vaccinated against Neisseria meningitidis.
11. 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 IMP
12. Sexually active female study participants of childbearing potential (ie, women who were not postmenopausal or who had not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male study participants (who had not been surgically sterilised by vasectomy) must have agreed to use effective contraception during the study and during the SFU Period of 40 days after the last dose of IMP. Postmenopausal women were, for the purposes of the protocol, defined as women who had not had menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may have been used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement was insufficient.

Exclusion criteria

Study participants who met any of the following exclusion criteria must have been excluded from the study:

1. Thymectomy within 12 months prior to Baseline or scheduled to occur during the 12-week study
2. Abnormal thyroid function as determined by local standard
3. Known positive serology for muscle-specific kinase
4. Minimal Manifestation Status of gMG based on the clinical judgement of the Investigator
5. Fixed weakness (‘burnt out’ gMG) based on the clinical judgement of the Investigator
6. History of meningococcal disease

7. Current or recent systemic infection within 2 weeks prior to Baseline or infection requiring iv antibiotics within 4 weeks prior to baseline
8. Pregnant, planning to become pregnant, or nursing female study participants
9. Recent surgery requiring general anaesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anaesthesia during the 12-week Treatment Period
10. Prior treatment with a complement inhibitor
11. Treatment with an experimental drug within 30 days or 5 half-lives of the experimental drug (whichever was longer) prior to baseline
12. Treatment with rituximab within 12 months prior to Baseline or planned to occur during the 12-week study (this exclusion criterion was implemented out of an abundance of caution, in the absence of data showing that complement inhibition in the context of B-cell elimination by rituximab is safe)
13. Treatment with IVIG, SC immunoglobulin, or PLEX 4 weeks prior to Baseline
14. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (study participants with a history of malignancy who had undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence were allowed)
15. History of or current significant medical disorder, psychiatric disorder, or laboratory abnormality that in the opinion of the Investigator would make the study participant unsuitable for participation in the study
16. Participation in another concurrent clinical study involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted)
17. Unable or unwilling to comply with the requirements of the study
18. Hypersensitivity to ZLP, any of its excipients, or to placebo

- **Treatments**

Study participants who met all entry criteria were randomised to receive daily SC doses of ZLP 0.3mg/kg/day or placebo. IMP was provided in prefilled syringes for self-injection using weight-bracketed dosing.

Table 15: ZLP dose presentations by weight brackets

Minimum (nominal) target dose (mg/kg)	**Actual dose (mg)**	**Weight range (kg)**	**Dose range (mg/kg)**
0.3	16.6	≥43 to <56	0.30 to 0.39
0.3	23.0	≥56 to <77	0.30 to 0.41
0.3	32.4	≥77 to 150	0.22 to 0.42

All standard of care therapy medications for gMG should have been kept at the same dose throughout the study, including corticosteroids and IST drugs. If escalation of gMG therapy (ie, 'rescue therapy') became necessary due to major deterioration of a study participant's clinical status, or risk of MG crisis as per the Investigator's judgment, the study participant may have received IVIG or PLEX treatment as 'rescue therapy.'

- **Objectives**

The primary objective of MG0010 was to confirm the efficacy of ZLP in study participants with gMG.

The secondary objective of MG0010 was the following: Confirmation of the safety and tolerability of ZLP in study participants with gMG

- **Outcomes/endpoints**

Primary endpoint

The null statistical hypothesis for the primary endpoint was that the treatment difference between ZLP and placebo in CBL to Week 12 in MG-ADL score was zero. The alternative statistical hypothesis was that the treatment difference between ZLP and placebo in CBL to Week 12 in MG-ADL score was different from zero.

Secondary endpoints

The key secondary endpoints were:

• CBL to Week 12 in the QMG score

• CBL to Week 12 in the MGC score

• CBL Week 12 in the MG-QOL15r score

The additional secondary endpoints were:

• Time to first administration of rescue therapy over the 12-week Treatment Period

• Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy

• Achieving a ≥ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy

• Achieving a ≥ 5-point reduction in QMG Score at Week 12 without rescue therapy

- **Sample size**

Initially the planned enrolment was approximately 130 subjects. The sample size estimation was based on the primary endpoint, CBL to week 12 in MG-ADL score, assuming a difference between treatment arms of 2.3 and a standard deviation of 3.4 based on the phase 2 study RA101495-02.201 (MG0009). With 65 subjects per treatment group, a 2-sided alpha of 0.05 and assumed rates of rescue and dropout of up to 10% and 5%, respectively, power was approximately 94%.

With global amendment 1 (Clinical study protocol (CSP) version 2.0, 18 December 2020) and statistical analysis plan (SAP) amendment 1 (01 February 2021) the total sample size was increased to account for a higher variability in the primary endpoint than what had originally been assumed and to maintain the power of the study. The new sample size calculation used a standard deviation of 3.7 and implied a total sample size of 156 subjects, 78 per treatment arm.

- **Randomisation and Blinding (masking)**

Subjects who met all entry criteria were to be randomised in a 1:1 ratio at baseline (Day 1) to receive 0.3 mg/kg zilucoplan or placebo administered SC. Randomisation was to be performed in a blinded fashion using a computerised randomisation algorithm and was stratified based on the baseline MG-ADL Score (≤9 versus ≥10), QMG Score (≤17 versus ≥18), and geographical region (North America, Europe, and Japan).

This was a double-blind study and subjects, and study staff was to remain blinded to treatment assignments until after the data had been cleaned, locked, and unblinded. Randomised subjects were to

receive 0.3 mg/kg zilucoplan or matching placebo administered SC at the Day 1 visit. Following in-clinic education and training, all subjects were to self-inject daily SC doses of blinded study drug, according to randomised treatment allocation. Single-use pre-filled syringes in injection devices were to be provided for use during the study. Matching placebo for the 0.3 mg/kg dose was to be provided in one presentation of 0.574 mL.

- **Statistical methods**

Once all subjects had completed the Day 84 visit, the study database was to be locked (interim database lock), unblinded, and the analyses for the study performed. If necessary, a final database lock was to occur once all the subjects had completed the study after the safety follow-up visit.

The SAP version 1.0 was approved 6 Nov 2019. There were five SAP amendments. The last/latest version (version 5.0) was dated 06 Dec 2021.

Primary estimand

The analysis of the primary efficacy endpoint utilised an estimand as follows:

Treatment: ZLP administered by daily SC injection (0.3mg/kg) versus placebo
Target population: adults with gMG according to study inclusion and exclusion criteria
Endpoint: CBL to Week 12 in MG-ADL score

Intercurrent event (ICE) handling:

• Administration of rescue therapy (ICE1): It was assumed to be a treatment failure from the time of the ICE.

• Any death or myasthenic crisis (ICE2): It was assumed to be a treatment failure from the time of the ICE.

• Any other monotone missing data (ICE3) were assumed to be missing at random (MAR): It was assumed that the study participant had remained on their IMP throughout the study (i.e., a "hypothetical-strategy" assuming study participants did not discontinue the study and remained on treatment).

Primary analysis

The primary efficacy analysis population was the mITT Population including all randomised participants who received at least 1 dose of study drug and had at least 1 post-dosing/baseline assessment.

For the primary efficacy endpoint, CBL to week 12 in MG-ADL score, treatment group differences were assessed using a mixed model with repeated measures (MMRM) ANCOVA with treatment, baseline MG-ADL score, baseline QMG score, geographical region, treatment-by-visit, baseline MG-ADL score-by-visit as fixed effects and subject as a random effect. The MMRM ANCOVA was to include Weeks 1, 2, 4, 8, and 12. The least square means (LSMs) and standard errors of each treatment group, and the LSM differences between zilucoplan, and placebo were to be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs and p-values.

Missing or censored data was to be imputed by the baseline or the last available MG-ADL score (including unscheduled visit), whichever was worse from the time after a participant had received rescue therapy (ICE1) and after a participant had died or experienced a myasthenic crisis (ICE2). Any other monotone missing data (ICE3) were to be assumed to be MAR. If a MG-ADL assessment was performed on the rescue therapy visit, then this as to be considered as the last score available prior to rescue therapy.

Continuous secondary efficacy endpoints (i.e., week 12 CBL in QMG Score, MGC Score, and MG-QOL15r Survey) were analysed using a MMRM ANCOVA. Overall, the analysis model and the approach were to be similar as compared with the primary endpoint analysis. As for the primary endpoint, data after use

of rescue therapy (ICE1) and death or myasthenic crisis (ICE2) were to be imputed by baseline or the last available corresponding score (including unscheduled visit), whichever was worse. Any other monotone missing data (ICE3) were to be assumed to be MAR.

The dichotomous secondary efficacy endpoints: achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy, a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy, and a ≥5-point reduction in QMG Score at Week 12 without rescue therapy were to be analysed by a logistic regression. Multiple imputation was used to impute missing at random data. Intermittent missing data were to be imputed using Markov Chain Monte Carlo to obtain monotone missing pattern. Any monotone missing data was to be imputed using MAR assumption. Endpoints were then dichotomised at Week 12 from the imputed continuous endpoint. Participants who received rescue therapy or who had an event of death or myasthenic crisis were to be considered as non-responders.

Time to receive rescue therapy over the 12-week treatment period was analysed using Kaplan-Meier plots. Subjects who did not take rescue therapy were censored at the date of withdrawal/study completion. The treatment difference was tested using a log Rank test.

Secondary Endpoints and multiplicity defined in SAP amendment 3 (dated 17 June 2021)

Control of the familywise type I error rate at a 2-sided alpha level of 0.05 was to be achieved using a parallel gatekeeping testing framework with different testing procedure for each of two endpoint families. Testing of secondary endpoints was only to proceed provided the primary endpoint was statistically significant at a 2-sided type 1 error of 0.05.

Family 1 included the key secondary endpoints and testing was performed using a fixed-sequential testing procedure in the following order:

1. CFB to Week 12 in the QMG score
2. CFB to Week 12 in the MGC score
3. CFB to Week 12 in the MG-QOL15r Survey

If all secondary endpoints in Family 1 were statistically significant at 2-sided type 1 error of 5%, family 2 was to be tested using a Holm procedure at 2-sided type 1 error of 0.05. Family 2 included the following secondary endpoints:

- Time to receive rescue therapy over the 12-week Treatment Period
- Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy
- Achieving a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy
- Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy

Sensitivity and supplementary analyses

Among the pre-planned sensitivity analyses was a MMRM analysis using a jump-to-reference (J2R) approach and a Tipping point analysis.

Among pre-planned supplementary analyses was a MMRM analysis applying a treatment policy approach where all data were to be used regardless of any ICE (i.e., no data was to be censored). Any missing MG-ADL score was to be handled based on the maximum likelihood estimation method under the MAR assumption.

Interim Analysis

Not Applicable.

Results

- **Participant flow**

A total of 239 study participants were screened at 75 sites (37 sites in North America, 27 sites in Europe, and 11 sites in the East Asia) and were included in the study; 25 study participants were screened prior to the COVID-19 pandemic period and 214 study participants were screened during the COVID-19 pandemic period. Of the 239 study participants who were screened, 63 study participants (26.4%; 4 study participants prior to the COVID-19 pandemic period and 59 study during the COVID-19 pandemic period) were deemed ineligible and were screen failures. Two of the 239 study participants who were screened (0.8%) withdrew prior to randomisation, both of whom withdrew prior to the COVID-19 pandemic period. The remaining 174 study participants were randomised and included in the mITT Population.

Table 16: Disposition and primary discontinuation reasons – Overall (mITT Population) MG0010

Category	**Placebo N=88 n (%)**	**ZLP 0.3mg/kg N=86 n (%)**	**All study participants N=174 n (%)**
Started study	88 (100)	86 (100)	174 (100)
Completed study	84 (95.5)	82 (95.3)	166 (95.4)
Discontinued	4 (4.5)	4 (4.7)	8 (4.6)
Primary reason for discontinuation			
Adverse event	0	2 (2.3)	2 (1.1)
Lost to follow up	0	0	0
Withdrawal by study participant	2 (2.3)	1 (1.2)	3 (1.7)
Physician decision	1 (1.1)	0	1 (0.6)
Protocol violation	0	0	0
Death	1 (1.1)	1 (1.2)	2 (1.1)
Safety reasons as determined by the Investigator or Sponsor	0	0	0
Intolerability of IMP	0	0	0
Other	0	0	0
Entered MG0011	84 (95.5)	81 (94.2)	165 (94.8)

- **Recruitment**

First study participant was enrolled 17 Sep 2019 and last study participant completed 30 Dec 2021. The study was conducted at 75 sites (37 sites in North America [Canada and the United States], 27 sites in Europe [France, Germany, Italy, Norway, Poland, Spain, and the United Kingdom], and 11 sites in the East Asia [Japan]).

- **Conduct of the study**

The original protocol (version 1.0) was dated 08 Apr 2019. There were 8 local amendments and one global protocol amendment: protocol amendment version 2.0 (18 Dec 2020). The following, among other, changes to the protocol were implemented:

- The total sample size was increased from 130 study participants to 156 study participants to account for higher variability in the primary endpoint than originally assumed.
- An unblinded interim analysis was added to be performed after the final study participant had completed the Week 12 Visit, or after the final study participant had prematurely discontinued prior to reaching Week 12. The purpose of this interim analysis was to analyse all available data to prepare regulatory submissions for approval of the gMG target indication.
- COVID-19 related amendments

- **Baseline data**

Table 17: Demographic characteristics- Overall (mITT population) MG0010

Variable **Statistic**	**Placebo** **N=88**	**ZLP** **0.3mg/kg** **N=86**	**All study participants** **N=174**
Sex, n (%)			
Female	47 (53.4)	52 (60.5)	99 (56.9)
Male	41 (46.6)	34 (39.5)	75 (43.1)
Race, n (%)			
American Indian or Alaska Native	1 (1.1)	0	1 (0.6)
Asian	14 (15.9)	7 (8.1)	21 (12.1)
Black	7 (8.0)	6 (7.0)	13 (7.5)
Native Hawaiian or other Pacific Islander	0	0	0
White	62 (70.5)	66 (76.7)	128 (73.6)
Other/Mixed	0	0	0
Missing	4 (4.5)	7 (8.1)	11 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	5 (5.7)	7 (8.1)	12 (6.9)
Not Hispanic or Latino	79 (89.8)	72 (83.7)	151 (86.8)
Missing	4 (4.5)	7 (8.1)	11 (6.3)
Region, n (%)			
East Asia	9 (10.2)	7 (8.1)	16 (9.2)
Europe	33 (37.5)	34 (39.5)	67 (38.5)
North America	46 (52.3)	45 (52.3)	91 (52.3)
Age (years)			
N	88	86	174
Mean (SD)	53.3 (15.7)	52.6 (14.6)	53.0 (15.1)
Median	55.5	54.5	55.0
Min, max	19, 75	21, 75	19, 75
Age group, n (%)			

≤18 years	0	0	0
19 years to <65 years	62 (70.5)	64 (74.4)	126 (72.4)
≥65 years	26 (29.5)	22 (25.6)	48 (27.6)
Weight (kg)			
N	88	86	174
Mean (SD)	88.2 (26.58)	90.1 (22.87)	89.1 (24.77)
Median	87.0	85.5	86.5
Min, max	41, 169	50, 145	41, 169
Weight (kg), n (%)			
<56	6 (6.8)	5 (5.8)	11 (6.3)
56 to <77	25 (28.4)	21 (24.4)	46 (26.4)
77 to <150	54 (61.4)	60 (69.8)	114 (65.5)
≥150	3 (3.4)	0	3 (1.7)
Height (cm)			
N	88	86	174
Mean (SD)	169.52 (9.98)	169.25 (10.51)	169.39 (10.21)
Median	168.00	168.00	168.00
Min, max	150.0, 200.0	147.6, 193.0	147.6, 200.0
BMI (kg/m^2)			
N	88	86	174
Mean (SD)	30.5 (8.02)	31.4 (7.22)	31.0 (7.63)
Median	29.0	30.5	30.0
Min, max	16, 54	19, 50	16, 54

There were no notable differences in demographics for the mITT Population by COVID-19 period. Baseline demographic characteristics for the per protocol set and safety set were consistent with those for the mITT Population.

Table 18: Baseline disease characteristics and gMG disease history – Overall (mITT Population) MG0010

Variable **Statistic**	**Placebo** **N=88**	**ZLP** **0.3mg/kg** **N=86**	**All** **Study** **participants** **N=174**
MGFA class at Screening, n (%)			
Class II	27 (30.7)	22 (25.6)	49 (28.2)
Class III	57 (64.8)	60 (69.8)	117 (67.2)
Class IV	4 (4.5)	4 (4.7)	8 (4.6)
Age at disease onset (years)			
N	88	85	173
Mean (SD)	44.02 (18.67)	43.47 (17.35)	43.75 (17.98)

Median	44.50	43.00	44.00
Min, max	9.0, 73.0	13.0, 73.0	9.0, 73.0
Duration of disease (years)			
N	88	86	174
Mean (SD)	8.96 (10.43)	9.34 (9.47)	9.15 (9.94)
Median	4.75	5.55	5.00
Min, max	0.2, 51.9	0.1, 42.3	0.1, 51.9
Symptoms at onset, n (%)			
Ocular	34 (38.6)	28 (32.6)	62 (35.6)
Generalised	54 (61.4)	58 (67.4)	112 (64.4)
Prior thymectomy, n (%)	37 (42.0)	45 (52.3)	82 (47.1)
Prior MG crisis, n (%)	29 (33.0)	28 (32.6)	57 (32.8)
Time since most recent crisis (months) [a]			
N	29	28	57
Mean (SD)	72.26 (109.76)	75.61 (91.81)	73.91 (100.45)
Median	21.98	38.98	26.94
Min, max	1.4,469.8	1.4, 277.6	1.4, 469.8
gMG refractory, n(%) [b]	44 (50.0)	44 (51.2)	88 (50.6)
Baseline MG-ADL score			
N	88	86	174
Mean (SD)	10.9 (3.4)	10.3 (2.5)	10.6 (3.0)
Median	10.5	10.0	10.0
Min, max	6, 19	6, 16	6, 19
Baseline MG-ADL score, n (%)			
≤9	33 (37.5)	33 (38.4)	66 (37.9)
≥10	55 (62.5)	53 (61.6)	108 (62.1)
Baseline QMG score			
N	88	86	174
Mean (SD)	19.4 (4.5)	18.7 (3.6)	19.1 (4.1)
Median	18.5	18.0	18.0
Min, max	13, 36	12, 31	12, 36
Baseline QMG score, n (%)			
≤17	38 (43.2)	38 (44.2)	76 (43.7)
≥18	50 (56.8)	48 (55.8)	98 (56.3)

a) Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12).
b) A study participant was considered "gMG Refractory" if they met the following criteria:
(1) Treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, or other corticosteroids, or
(2) History of treatment with at least 1 of the therapies listed in (1) for 1 year or more and required chronic plasma exchange or IVIG or SCIG at least every 3 months for the 12 months prior to enrolment.

The usage of Baseline gMG-specific medications was generally balanced between treatment groups.

Table 19: Baseline gMG-specific medications (SS)

Group **Concomitant** **Preferred term**	**Placebo N=88 n (%)**	**ZLP 0.3mg/kg N=86 n (%)**	**All study participants N=174 n (%)**
Any gMG-specific Baseline medications	83 (94.3)	84 (97.7)	167 (96.0)
Group A	51 (58.0)	59 (68.6)	110 (63.2)
Prednisone for gMG	33 (37.5)	38 (44.2)	71 (40.8)
Prednisone	33 (37.5)	38 (44.2)	71 (40.8)
Other corticosteroids for gMG	18 (20.5)	21 (24.4)	39 (22.4)
Prednisolone	16 (18.2)	20 (23.3)	36 (20.7)
Methylprednisolone	2 (2.3)	1 (1.2)	3 (1.7)
Group B	35 (39.8)	30 (34.9)	65 (37.4)
Azathioprine	18 (20.5)	13 (15.1)	31 (17.8)
Azathioprine	18 (20.5)	13 (15.1)	31 (17.8)
Mycophenolate	17 (19.3)	17 (19.8)	34 (19.5)
Mycophenolate mofetil	17 (19.3)	17 (19.8)	34 (19.5)
Group C	0	0	0
IVIG	0	0	0
Immunoglobulins NOS	0	0	0
SCIG	0	0	0
Immunoglobulins NOS	0	0	0
Group D	0	0	0
IVIG, SCIG, or PLEX	0	0	0
Immunoglobulins NOS	0	0	0
PLEX	0	0	0
Group E	15 (17.0)	12 (14.0)	27 (15.5)
Cyclosporine	7 (8.0)	6 (7.0)	13 (7.5)
Ciclosporin	7 (8.0)	6 (7.0)	13 (7.5)
Cyclophosphamide	0	0	0
Cyclophosphamide	0	0	0
Methotrexate	1 (1.1)	3 (3.5)	4 (2.3)
Methotrexate	1 (1.1)	3 (3.5)	4 (2.3)
Tacrolimus	7 (8.0)	3 (3.5)	10 (5.7)
Tacrolimus	7 (8.0)	3 (3.5)	10 (5.7)
Rituximab	0	0	0
Rituximab	0	0	0
Group F	73 (83.0)	74 (86.0)	147 (84.5)
Cholinesterase inhibitors	73 (83.0)	74 (86.0)	147 (84.5)
Ambenonium	3 (3.4)	4 (4.7)	7 (4.0)
Pyridostigmine	70 (79.5)	70 (81.4)	140 (80.5)

gMG=generalised myasthenia gravis; IVIG=intravenous immunoglobulin; NOS=not otherwise specified; PLEX=plasma exchange; SCIG=subcutaneous immunoglobulin; SS=Safety Set; ZLP=zilucoplan

Note: Baseline medications include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).

- **Numbers analysed**

Table 20: Analysis sets

Analysis set	Placebo N=88 n (%)	ZLP 0.3mg/kg N=86 n (%)	All study participants N=174 n (%)
RS	88 (100)	86 (100)	174 (100)
mITT Population	88 (100)	86 (100)	174 (100)
CFS	81 (92.0)	77 (89.5)	158 (90.8)
PPS	77 (87.5)	70 (81.4)	147 (84.5)
SS	88 (100)	86 (100)	174 (100)
PK-PPS	88 (100)	85 (98.8)	173 (99.4)
PD-PPS	88 (100)	85 (98.8)	173 (99.4)

CFS=COVID-19 Free Set; COVID-19=coronavirus disease 2019; mITT=modified Intent-to-Treat; PD-PPS=Pharmacodynamic Per-Protocol Set; PK-PPS=Pharmacokinetic Per-Protocol Set; PPS=Per Protocol Set; RS=Randomised Set; SS=Safety Set; ZLP=zilucoplan

- **Outcomes and estimation**

The LSM CBL through Week 12 in MG-ADL score using MMRM ANCOVA is presented for the mITT Population in the figure below. The changes from Baseline to Week 12 in the primary (MG-ADL) and key secondary (QMG, MGC, MG-QOL15r) efficacy endpoints are shown in the table below.

Figure 10: MG0010 – LS mean change from baseline to week 12 in MG-ADL score (mITT Population [MMRM ANCOVA])

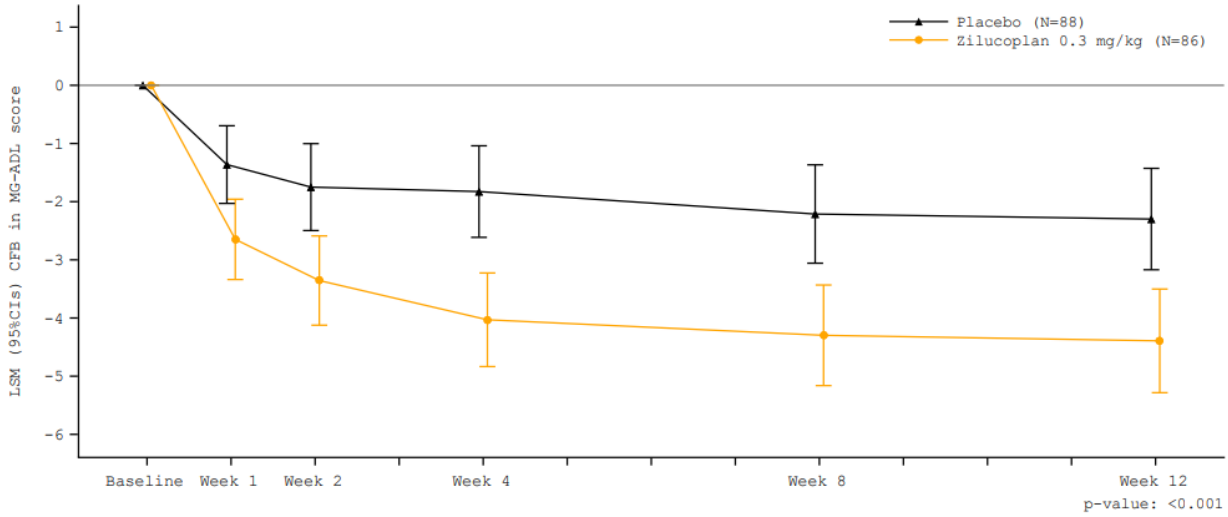


Table 21: MG0010 – change from baseline to week 12 in primary and key secondary efficacy endpoints (mITT Population [MMRM ANCOVA])

Visit **Statistic**	**Placebo** **N=88**	**ZLP** **0.3mg/kg** **N=86**
Week 12 **MG-ADL**		
LS mean (SE)	-2.30 (0.44)	-4.39 (0.45)
95% CI	-3.17, -1.43	-5.28, -3.50
LS mean difference (SE)	-	-2.09 (0.58)
95% CI	-	-3.24, -0.95
p-value	-	<0.001
Week 12 **QMG**		
LS mean (SE)	-3.25 (0.55)	-6.19 (0.56)
95% CI	-4.32, -2.17	-7.29, -5.08
LS mean difference (SE)	-	-2.94 (0.73)
95% CI	-	-4.39, -1.49
p-value	-	<0.001
Week 12 **MGC**		
LS mean (SE)	-5.42 (0.79)	-8.62 (0.81)
95% CI	-6.98, -3.86	-10.22, -7.01
LS mean difference (SE)	-	-3.20 (1.03)
95% CI	-	-5.24, -1.16
p-value	-	0.0023
Week 12 **MG-QOL15r**		
LS mean (SE)	-3.16 (0.76)	-5.65 (0.77)
95% CI	-4.65, -1.67	-7.17, -4.12
LS mean difference (SE)	-	-2.49 (0.99)
95% CI	-	-4.45, -0.54
p-value	-	0.0128

Sensitivity and supplementary analyses – primary endpoint

When the primary efficacy endpoint was analysed using MMRM ANCOVA with the J2R approach, the LSM CBL to Week 12 in MG-ADL score was -4.47 in the ZLP 0.3mg/kg treatment group and -2.44 in the placebo treatment group, LSM difference of -2.03 (nominal p<0.001).

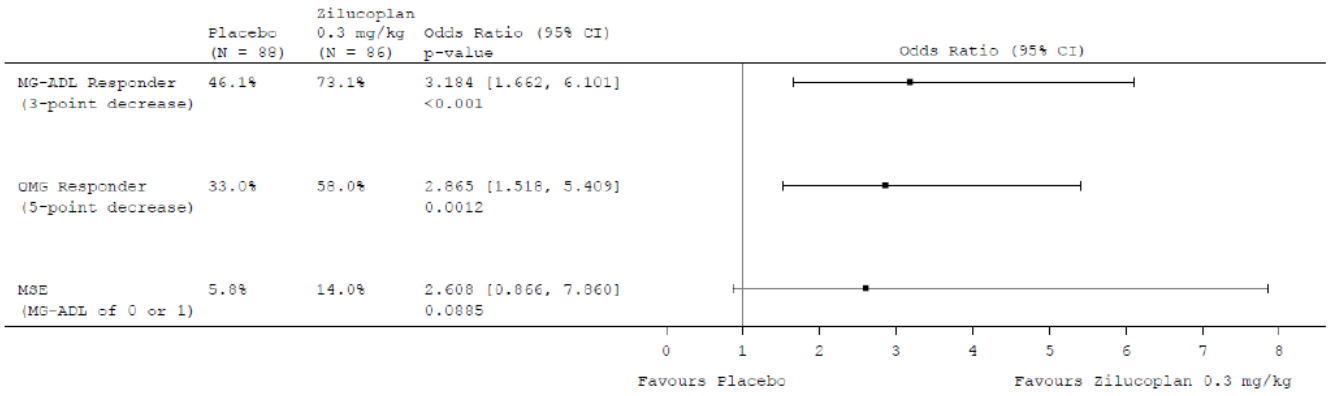
When the primary efficacy endpoint was analysed using MMRM ANCOVA applying a treatment policy strategy, the LSM CBL to Week 12 in MG-ADL score was -4.56 in the ZLP 0.3mg/kg treatment group and -2.54 in the placebo treatment group, LSM difference of -2.02 (nominal p<0.001).

Other secondary endpoints (Family 2)

The proportion of study participants in the ZLP 0.3mg/kg treatment group compared with the placebo treatment group was higher with odds ratios significantly favouring ZLP treatment over placebo for MG-

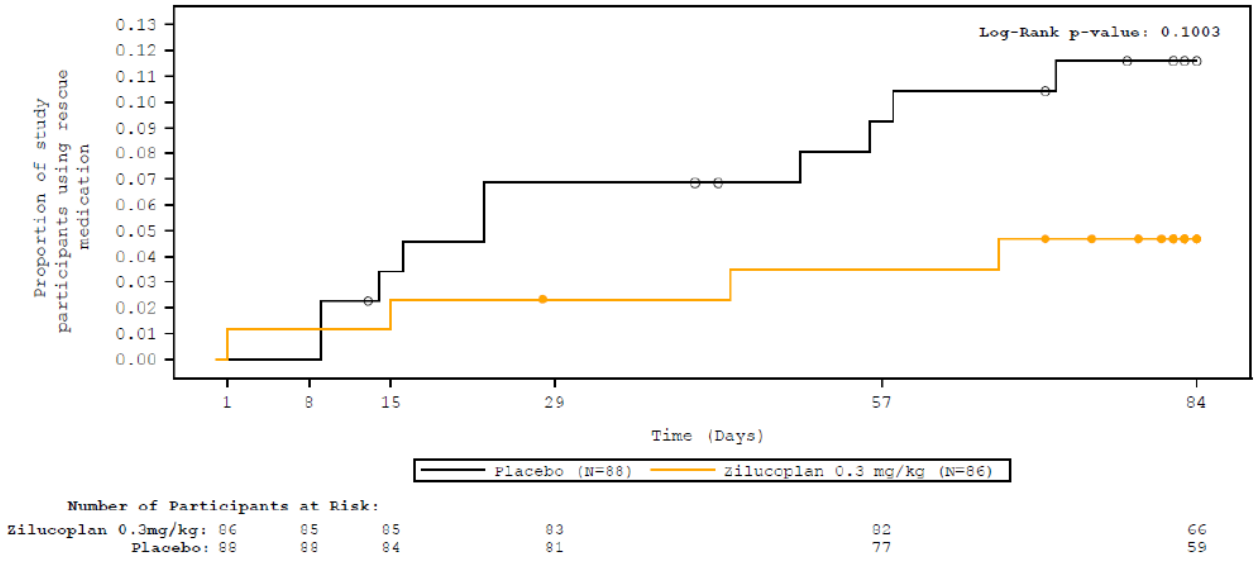
ADL responders (73.1% vs 46.1%, respectively; OR: 3.184; 95% CI: 1.662 to 6.101) and QMG responders (58.0% vs 33.0%, respectively; odds ratio: 2.865; 95% CI: 1.518 to 5.409).

Figure 11: Forest plot of MG-ADL responders, QMG responders, and MSE at Week 12 (mITT Population) MG0010



The cumulative proportion of study participants receiving rescue therapy by Week 12 was lower in the ZLP 0.3mg/kg treatment group (Day 84: 4 study participants [5%]) compared with the placebo treatment group (Day 84: 10 study participants [12%]). This difference favoured ZLP numerically but was not statistically significant (p=0.1003).

Figure 12: Kaplan-Meier plot of time to rescue therapy (mITT Population) MG0010



Note: Circles represent censored study participants

- **Ancillary analyses**

A summary of MG-ADL score and CBL is provided for the mITT Population by subgroup and by visit in the table below.

Table 22: Subgroup analysis of change from Baseline to Week 12 in MG-ADL (mITT Population) MG0010

Subgroup	**Placebo N=88**		**ZLP 0.3mg/kg N=86**	
	n	**Mean CFB (SD)**	**n**	**Mean CFB (SD)**
Overall CFB Week 12	85	-2.85 (3.60)	84	-4.70 (3.93)
Age				
<65 years	59	-2.75 (3.83)	63	-4.56 (4.14)
≥65 years	26	-3.08 (3.07)	21	-5.14 (3.24)
Gender				
Male	40	-2.85 (3.62)	33	-5.12 (3.62)
Female	45	-2.84 (3.62)	51	-4.43 (4.12)
Duration of disease at Baseline				
<Median	46	-3.04 (3.71)	39	-3.92 (3.59)
≥Median	39	-2.62 (3.51)	45	-5.38 (4.12)
MGFA disease class at Baseline				
Class II (IIa, IIb)	26	-3.69 (3.60)	22	-4.23 (3.26)
Class III (IIIa, IIIb)	55	-2.42 (3.44)	58	-4.69 (3.96)
Class IV (IVa or IVb)	4	-3.25 (5.74)	4	-7.50 (6.45)
Baseline MG-ADL				
≤9	31	-2.48 (2.97)	33	-3.88 (2.76)
≥10	54	-3.06 (3.93)	51	-5.24 (4.47)
Baseline QMG				
≤17	37	-2.81 (3.93)	37	-4.19 (3.08)
≥18	48	-2.88 (3.37)	47	-5.11 (4.47)
MG refractory				
Yes	42	-2.26 (3.39)	44	-4.89 (4.09)
No	43	-3.42 (3.75)	40	-4.50 (3.78)
Ever had a crisis				
Yes	28	-4.14 (4.01)	28	-5.54 (3.98)
No	57	-2.21 (3.23)	55	-4.44 (3.74)
Prior thymectomy				
Yes	36	-2.78 (3.64)	43	-5.02 (4.32)
No	49	-2.90 (3.61)	41	-4.37 (3.48)
Prior steroid therapy				
Yes	72	-3.00 (3.74)	75	-4.88 (3.95)
No	13	-2.00 (2.65)	9	-3.22 (3.60)
Steroid therapy taken at Baseline				

Yes	50	-2.80 (3.84)	59	-4.58 (3.59)
No	35	-2.91 (3.28)	25	-5.00 (4.69)
Prior immunosuppressive therapy (nonsteroidal)				
Yes	31	-1.71 (3.47)	26	-4.62 (4.45)
No	54	-3.50 (3.54)	58	-4.74 (3.71)
Immunosuppressive therapy (nonsteroidal) at Baseline				
Yes	15	-1.07 (2.25)	12	-3.83 (4.09)
No	70	-3.23 (3.73)	72	-4.85 (3.91)
Prior history of IVIG or sc immunoglobulin or PLEX				
Yes	62	-2.94 (3.97)	57	-4.93 (4.05)
No	23	-2.61 (2.41)	27	-4.22 (3.68)
Diagnosed with thymoma				
Yes	18	-2.61 (4.00)	20	-5.80 (3.19)
No	67	-2.91 (3.52)	64	-4.36 (4.09)

Table 23: Subgroup analysis of change from baseline to week 12 in QMG (mITT Population) MG0010

Subgroup Category	**Placebo N=88**		**ZLP 0.3mg/kg N=86**	
	n	**Mean CFB (SD)**	**n**	**Mean CFB (SD)**
Overall CFB Week 12	84	-3.38 (4.21)	83	-6.31 (4.92)
Age				
<65 years	58	-3.17 (4.15)	62	-6.35 (5.21)
≥65 years	26	-3.85 (4.37)	21	-6.19 (4.04)
MGFA disease class at Baseline				
Class II (IIa, IIb)	26	-3.65 (3.88)	22	-5.86 (5.13)
Class III (IIIa, IIIb)	54	-3.24 (4.41)	57	-6.44 (4.83)
Class IV (IVa or IVb)	4	-3.50 (4.43)	4	-7.00 (6.27)
Baseline MG-ADL				
≤9	30	-2.87 (4.11)	33	-6.03 (4.91)
≥10	54	-3.67 (4.27)	50	-6.50 (4.96)
Baseline QMG				
≤17	37	-2.43 (3.88)	37	-5.70 (3.98)
≥18	47	-4.13 (4.34)	46	-6.80 (5.56)

Table 24: Subgroup analysis of change from baseline to week 12 in MGC (mITT Population) MG0010

Subgroup Category	**Placebo N=88**		**ZLP 0.3mg/kg N=86**	
	n	**Mean CFB (SD)**	**n**	**Mean CFB (SD)**
Overall CFB at Week 12	84	-6.58 (6.46)	83	-9.20 (6.35)
Age				
<65 years	58	-6.67 (6.53)	62	-9.13 (6.81)
≥65 years	26	-6.38 (6.43)	21	-9.43 (4.87)
MGFA disease class at Baseline				
Class II (IIa, IIb)	26	-7.58 (5.68)	22	-9.82 (7.20)
Class III (IIIa, IIIb)	54	-6.15 (6.84)	57	-8.72 (5.98)
Class IV (IVa or IVb)	4	-6.00 (6.93)	4	-12.75 (6.95)
Baseline MG-ADL				
≤9	30	-5.43 (6.27)	33	-7.97 (5.49)
≥10	54	-7.22 (6.53)	50	-10.02 (6.78)
Baseline QMG				
≤17	37	-5.57 (5.70)	37	-7.97 (5.49)
≥18	47	-7.38 (6.95)	46	-10.20 (6.88)

Table 25: Subgroup analysis of change from baseline to week 12 in MG-QOL15r (mITT Population)

Subgroup Category	Placebo N=88		ZLP 0.3mg/kg N=86	
	n	Mean CFB (SD)	n	Mean CFB (SD)
Overall CFB at Week 12	83	-3.93 (6.34)	82	-6.09 (7.10)
Age				
<65 years	57	-3.65 (6.59)	62	-7.02 (7.60)
≥65 years	26	-4.54 (5.83)	20	-3.20 (4.23)
MGFA disease class at Baseline				
Class II (IIa, IIb)	25	-5.28 (6.54)	22	-4.95 (6.22)
Class III (IIIa, IIIb)	54	-3.56 (6.23)	57	-6.25 (7.12)
Class IV (IVa or IVb)	4	-0.50 (6.24)	3	-11.33 (12.58)
Baseline MG-ADL				
≤9	29	-3.79 (5.85)	33	-6.21 (5.38)
≥10	54	-4.00 (6.64)	49	-6.00 (8.11)
Baseline QMG				
≤17	36	-4.61 (6.68)	37	-5.73 (7.02)
≥18	47	-3.40 (6.09)	45	-6.38 (7.23)

Antidrug antibodies

By Week 12, 2 study participants each in the ZLP 0.3mg/kg treatment group and the placebo group were treatment-emergent ADA positive at 1 visit or more. In the 2 study participants in the ZLP 0.3mg/kg treatment group who were treatment-emergent ADA positive, the CBL in MG-ADL score was numerically greater compared with the study participants who were ADA negative.

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of Zilucoplan in subjects with generalized myasthenia gravis		
Study identifier	MG0010 (Ra Pharmaceuticals, Inc. RA101495-02.301 [RAISE]) EUDRACT 2019-001564-30 NCT04115293	
Design	Multicentre, Randomised, Double-Blind, Placebo-Controlled	
	Duration of main phase:	12 weeks
	Duration of Run-in phase:	Screening Period of up to 4 weeks
	Duration of Extension phase:	OLE in MG0011(Raise XT)
Hypothesis	Superiority to placebo	

Title: A phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of Zilucoplan in subjects with generalized myasthenia gravis

Study identifier	MG0010 (Ra Pharmaceuticals, Inc. RA101495-02.301 [RAISE]) EUDRACT 2019-001564-30 NCT04115293		
Treatments groups	Zilucoplan		Zilucoplan 0.3 mg/Kg administered daily by SC injection for a duration of 12 weeks Number randomised = 86
	Placebo		Placebo administered daily by SC injection for a duration of 12 weeks Number randomised =88
Endpoints and definitions	Primary endpoint	CFB to Week 12 in MG-ADL score	The MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity. Higher scores are associated with more severe symptoms of MG. A 2-point change in MG-ADL Score is considered clinically meaningful.
	Key secondary endpoint	CFB to Week 12 in the QMG score	The QMG test is a standardised quantitative strength scoring system and measures 13 items on a 0-3 scale, with 0 being the least severe. The total sum of the 13 items represents the QMG score. The QMG score can range from 0 (least severe) to 39 (most severe). A change in the QMG Score of 3 points may be considered clinically meaningful, in a typical clinical trial population of MG patients.
	Key secondary endpoint	CFB to Week 12 in the MGC score	The MGC is a 10-item scale that has been used to measure the clinical status of patients with Myasthenia Gravis (MG) in order to evaluate treatment response. The MGC has 4-point Likert-type scale response options ranging from 0 to 2, 3, 4, 5, 6 or 9 according to the item (weighted response options). The total score is the sum of all items (range 0-50) where higher scores indicate more severe impairment due to the disease.
	Key secondary endpoint	CFB to Week 12 in MG-QOL15r score	The MG-QOL15r is a 15-item survey that was designed to assess quality of life in patients with MG. The MG-QoL has 3-point Likert Scale response options ranging from 0 to 2. The MGQoL15r score can range from 0 to 30, where higher scores indicate more severe impact of the disease on aspects of the patient's life
Database lock	18-Jan-2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Comparison of zilucoplan 0.3 mg/kg treatment group versus placebo in CFB to Week 12 in MG-ADL Score at a 2-sided 0.05 significance level based on the mITT population using LSM.		
Descriptive statistics and estimate variability	Treatment group	placebo	zilucoplan
	Number of subject	88	86
	LS mean change	-2.30	-4.39
	95% CI	-3.17, -1.43	-5.28, -3.50
Effect estimate	Primary endpoint:	Comparison groups	Zilucoplan versus placebo

Title: A phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of Zilucoplan in subjects with generalized myasthenia gravis			
Study identifier	MG0010 (Ra Pharmaceuticals, Inc. RA101495-02.301 [RAISE]) EUDRACT 2019-001564-30 NCT04115293		
per comparison	CFB to Week 12 in MG-ADL Score	LS mean difference	-2.09
		95% CI	-3.24,-0.95
		p-value	<0.001
Notes	ICE handling: • Administration of rescue therapy (ICE1): will be assumed to be a treatment failure from the time of the ICE. • Any death or myasthenic crisis (ICE2) will be assumed to be a treatment failure from the time of the ICE. • Any other monotone missing data (ICE3) will be assumed to be missing at random: it is assumed that the participant had remained on their treatment throughout the study (i.e., a "Hypothetical strategy" assuming participants did not discontinue the study and remained on treatment).		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Comparison of zilucoplan 0.3 mg/kg treatment group versus placebo in CFB to Week 12 in QMG Score at a 2-sided 0.05 significance level based on the mITT population using LSM.		
Descriptive statistics and estimate variability	Treatment group	placebo	zilucoplan
	Number of subject	88	86
	LS mean change	-3.25	-6.19
	95% CI	-4.32, -2.17	-7.29, -5.08
Effect estimate per comparison	Secondary endpoint: CFB to Week 12 in QMG Score	Comparison groups	Zilucoplan versus placebo
		LS mean difference	-2.94
		95% CI	-4.39,-1.49
		p-value	<0.001
Analysis description	**Secondary analysis**		
Analysis population and time point description	Comparison of zilucoplan 0.3 mg/kg treatment group versus placebo in CFB to Week 12 in MGC Score at a 2-sided 0.05 significance level based on the mITT population using LSM.		
Descriptive statistics and estimate variability	Treatment group	placebo	zilucoplan
	Number of subject	88	86
	LS mean change	-5.42	-8.62
	95% CI	-6.98, -3.86	-10.22, -7.01
Effect estimate per comparison	Secondary endpoint: CFB to Week 12 in MGC Score	Comparison groups	Zilucoplan versus placebo
		LS mean difference	-3.20
		95% CI	-5.24,-1.16
		p-value	0.0023
Analysis description	**Secondary analysis**		
Analysis population and time point description	Comparison of zilucoplan 0.3 mg/kg treatment group versus placebo in CFB to Week 12 in MG-QOL15r Score at a 2-sided 0.05 significance level based on the mITT population using LSM.		
Descriptive statistics and estimate variability	Treatment group	placebo	zilucoplan
	Number of subject	88	86
	LS mean change	-3.16	-5.65

Title: A phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of Zilucoplan in subjects with generalized myasthenia gravis			
Study identifier	MG0010 (Ra Pharmaceuticals, Inc. RA101495-02.301 [RAISE]) EUDRACT 2019-001564-30 NCT04115293		
	95% CI	-4.65, -1.67	-7.17, -4.12
Effect estimate per comparison	Secondary endpoint: CFB to Week 12 in MG-QOL15r Score	Comparison groups	Zilucoplan versus placebo
		LS mean difference	-2.49
		95% CI	-4.45,-0.57
		p-value	0.0128

2.6.5.3. Clinical studies in special populations

In the controlled pivotal trial MG0010, 48 of 174 participants (27.6%) were aged ≥ 65years. In the controlled phase II trial MG009 7 of 45 participants (15.6%) were aged ≥ 65years. In the non-controlled OL trial MG0011, 57 of 200 participants (28.6%) were aged ≥ 65years (8 Sept data cut).

	Age 55-64 (Older subjects number /total number)	**Age 65-75 (Older subjects number /total number)**	**Age 75+ (Older subjects number /total number)**
Controlled Trials MG0010 N=45 MG0009 N=174	 15/45 40/174	 6/45 48/174	 1/45 0/174
Non Controlled trials MG0011 N=200	48/200	56/200	1/200

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Overview

A Model-Informed Analysis was performed intended to estimate the maintenance of efficacy effect versus placebo for up to 24 weeks using indirect comparison through a Main-Analytical Approach and a set of sensitivity, supplementary and secondary analyses. The Main Analytical Approach of this Model-Informed Analysis was a 2-part combined analysis of 12-week double-blind data from MG0009, MG0010, 24-weeks data from MG0011 of patients initially randomised to ZLP in MG0010 within a Bayesian Framework using a linear model with log time.

Part 1 synthesised the information based on the summary data on PB response over time through a meta-regression model using aggregate data (SLR, MG-Registry, Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX)).

In Part 2, a combined Bayesian analysis of the MG0009 and MG0010 double-blind studies and of the MG0011 open-label extension was done, using the posterior distributions that resulted from the analysis in Part 1, as informative priors in this analysis – downweighed by 30% (to reflect the choice of model assumptions and to account for unexpected features (as compared to the features of external studies) of MG0009 and MG0010).

In summary, the analysis of the summary level data was combined with the IPD (individual patient data) through a Bayesian framework in this two-part approach. This model assumed that the disease progression was similar over time in the PB and ZLP treatment groups.

Summary of methods

Multiple statistical methods were used to perform the model-informed analysis.

Regarding the external, historical data for placebo patients up to week 24, mixed models with repeated measures using an unstructured correlation structure (alt AR1) were used in patient-level data from external sources after using Inverse Probability Treatment Weighting (IPTW). Meta-regression on group-level data were applied to combine summary results from all external sources.

The primary analysis was a combined analysis of MG0009 and MG0010 within a Bayesian Framework using a linear model with log time based on down-weighted, informative priors from the analysis of external, historical data of placebo patients up to week 24. This model assumed that the disease progression was similar over time in the PB and ZLP treatment groups.

Bayesian statistics provided a formal mathematical method for combining prior information with current information observed in the clinical trial. This combined-studies analysis consisted of two parts; the meta-regression on PB summary data (sensitivity analyses were planned and included the use of vague prior) and the combined-IPD analysis informed by the results of the first part.

Part 1 synthesised the information based on the summary data on PB response over time through a meta-regression model using aggregate data. The outcome of this Bayesian meta-regression was the posterior distribution of the model parameters: the overall mean response (intercept), the slope of the response over time and the baseline effect.

In Part 2, a combined Bayesian analysis of the MG0009 and MG0010 studies was done, using the posterior distributions that resulted from the analysis in Part 1, as informative priors in this analysis. In other words, the analysis of the summary level data was combined with the IPD through the Bayesian framework in this two-part approach.

Primary results

At Week 24 the mean estimation of a population treatment effect for ZLP over placebo was -2.60 (95% CrI: [-3.70; -1.50]) on the MG-ADL scale as the primary endpoint. The probability that the posterior mean change from baseline in MG-ADL at Week 24 in zilucoplan is lower than the posterior mean CFB in MG-ADL in placebo was > 99.9%. The probability that the difference in posteriors mean CFB in MG-ADL between zilucoplan and placebo is lower than the clinically meaningful threshold of -2 was 85.8%. Moreover, the Main-Analytical Approach produced Week 12 results that were consistent the significant results observed in MG0010 when using all data through 24 weeks.

Sensitivity analysis, secondary analysis, supplemental analysis

A wide range of sensitivity, supplementary and secondary analyses were planned to assess the robustness of the results to all the assumptions made in the primary analysis (historical or vague prior, confidence in the prior if use of historical prior, use of long-term data or not, statistical model used to fit the data, etc.). According to the applicant, all analyses gave results that are consistent with the primary analysis.

2.6.5.5. Supportive study

Study MG0011

MG0011 is an ongoing, multicentre, open-label extension study evaluating the long-term safety, tolerability, and efficacy of ZLP in study participants with gMG who previously participated in a parent ZLP study (i.e., MG0009 or MG0010). To be eligible, subjects had to have successfully completed participation in a parent study. All subjects received ZLP 0.3mg/kg administered SC at the Day E1 Visit.

Study participants or caregivers were then instructed to self-inject daily SC doses of IMP for the subsequent doses. Weight-bracketed dosing strategy as in study MG0010 was applied.

The primary endpoint pertained to safety. Secondary endpoints were MG-ADL, QMG, MGC and MG-QOL15r.

It was expected that approximately 200 subjects would be enrolled from the parent studies, MG0009 and MG0010.

Efficacy analysis

No statistical testing was planned. Changes from Baseline to Week E12 in MG-ADL score and QMG score were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, geographical region, parent study factor, and baseline MG-ADL score-by-visit as fixed effects, and study participant as a random effect.

The MMRM ANCOVA included Week 1 to Week 12 (double-blind [parent study] Treatment Period) and Week E1 to Week E12 (open label [MG0011] Treatment Period) for groups of PB/ZLP 0.3mg/kg and ZLP 0.3/ZLP 0.3mg/kg. Separate models were fitted for each group.

The LSM of placebo/ZLP 0.3mg/kg and ZLP 0.3/ZLP 0.3mg/kg have been reported for all visits along with corresponding 2-sided 95% CIs. Statistical outputs such as LSM, and CI from Week 1 to Week E12 have been plotted in graphs.

Time to receive rescue therapy over the open-label treatment period was analysed as time-to-event, using Kaplan-Meier plots.

Missing total scores of QMG, MG-ADL, MGC, and MG-QOL15r were not imputed. In addition, data after rescue medication were not imputed.

The ITT Population was to include all enrolled subjects. The mITT Population was to include all subjects in the ITT population who had received study drug and had at least 1 post-dosing MG-ADL score.

Analyses were based on the randomised treatment in the parent study (i.e., MG0009 or MG0010) and the planned treatment in MG0011 (i.e., ZLP 0.3mg/kg) and have been displayed in summaries as follows:

- PB/ZLP 0.1/0.3mg/kg
- PB/ZLP 0.3mg/kg
- ZLP 0.1/ZLP 0.1/ZLP 0.3mg/kg
- ZLP 0.3/ZLP 0.3mg/kg
- All ZLP doses

Results

At the time of the clinical data cut-off, 199 study participants had been enrolled in MG0011. This included study participants who transitioned from MG0009 and all study participants who completed MG0010, with the exception of 1 study participant whose data is not included in the clinical data cut-off, because having entered MG0011 after the clinical data cut-off for this interim case study report.

Of the 199 study participants enrolled in the study, 158 study participants (79.4%) had completed the Week E12 Visit, although they may have remained ongoing.

Table 26: Disposition and discontinuation reasons (ITT Population) MG0011

Category	**Placebo/ZLP 0.1mg/kg/ 0.3mg/kg N=5 n (%)**	**Placebo/ ZLP 0.3mg/kg N=90 n (%)**	**ZLP 0.1mg/kg/ 0.1mg/kg/ 0.3mg/kg N=12 n (%)**	**ZLP 0.3mg/kg/ 0.3mg/kg N=92 n (%)**	**All ZLP doses N=199 n (%)**
Entered MG0011	5 (100)	90 (100)	12 (100)	92 (100)	199 (100)
Completed MG0011 Week E12	5 (100)	68 (75.6)	12 (100)	73 (79.3)	158 (79.4)
Ongoing	4 (80.0)	74 (82.2)	11 (91.7)	84 (91.3)	173 (86.9)
Discontinued	1 (20.0)	16 (17.8)	1 (8.3)	8 (8.7)	26 (13.1)
Primary reason for discontinuation					
Adverse event	0	4 (4.4)	0	0	4 (2.0)
Withdrawal by study participant	0	7 (7.8)	1 (8.3)	0	8 (4.0)
Physician decision	0	3 (3.3)	0	2 (2.2)	5 (2.5)
Death	0	1 (1.1)	0	4 (4.3)	5 (2.5)
Safety reasons as determined by the Investigator or Sponsor	0	1 (1.1)	0	0	1 (0.5)
Other	1 (20.0)	0	0	2 (2.2)	3 (1.5)

Efficacy outcomes

The LSM differences between Week E12 and Week 12 in the ZLP 0.3/ZLP 0.3mg/kg and PB/ZLP 0.3mg/kg treatment groups were -2.25 (-3.41, -1.10) and -3.39 (-5.85, -0.93), respectively, showing further reduction in MG-ADL score in both groups after Week 12 and the continued benefit of ZLP treatment.

Table 27: Change from parent study baseline to week E12 in MG-ADL score (mITT Population [MMRM ANCOVA]) MG0011

Visit Statistic	**Placebo/ ZLP 0.3mg/kg N=90**	**ZLP 0.3/ 0.3mg/kg N=92**
Week 12, n	90	92
Mean (SE)	-2.93 (0.38)	-4.79 (0.40)
Median	-3.00	-5.00
Min, max	-14.0, 4.0	-13.0, 4.0
LS mean (SE)	-2.93 (0.70)	-4.05 (0.54)
95% CI	[-4.31, -1.56]	[-5.11, -2.98]
Week E12, n	69	71
Mean (SE)	-6.22 (0.49)	-6.14 (0.43)
Median	-6.00	-6.00
Min, max	-14.0, 3.0	-15.0, 2.0
LS mean (SE)	-6.32 (0.84)	-6.30 (0.58)
95% CI	[-8.00, -4.65]	[-7.44, -5.15]
Difference between Week E12 versus parent study Week 12	-3.39	-2.25
95% CI	[-5.85, -0.93]	[-3.41, -1.10]
p-value [a]	0.0075	0.0002

a) The LSM difference presented was Open-Label Extension Weeks vs Double Blind Week in the parent study in MG0011.

Figure 13: Change from parent study baseline to week E12 in MG-ADL score (mITT Population) MG0011

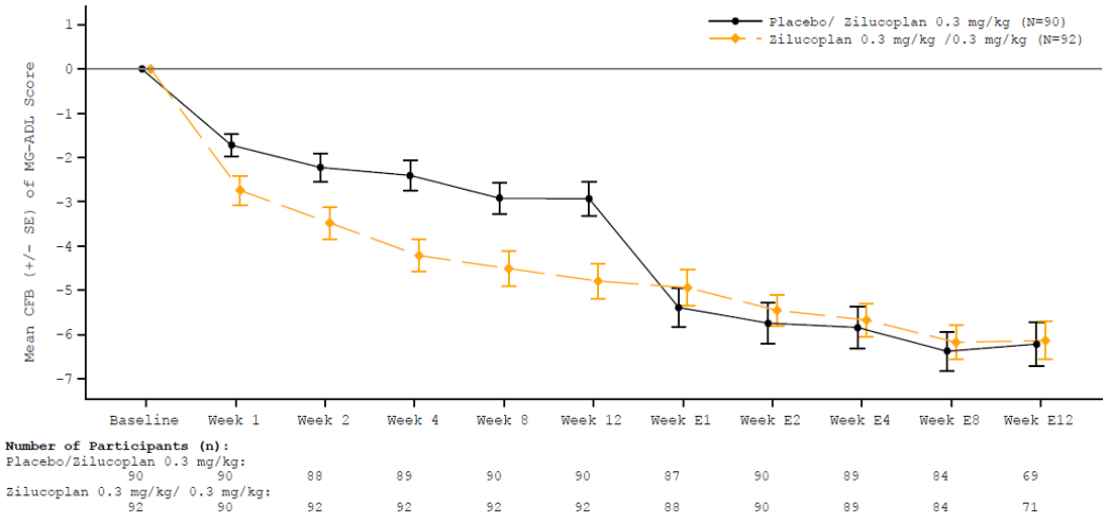


Table 28: Change from parent study baseline to week E12 in QMG, MGC and MG-QOL15r score (mITT Population [MMRM ANCOVA]) MG0011

Visit Statistic	**Placebo/ ZLP 0.3mg/kg N=90**	**ZLP 0.3/0.3mg/kg N=92**
Week 12 **QMG**, n	89	91
LS mean (SE)	-3.20 (0.82)	-7.04 (0.74)
95% CI	[-4.82, -1.58]	[-8.51, -5.58]
Week E12, n	68	69
LS mean (SE)	-8.52 (1.19)	-8.87, (0.73)
95% CI	[-10.89, -6.16]	[-10.31, -7.42]
Difference between Week E12 versus parent study Week 12	-5.33	-1.82
95% CI	[-8.54, -2.12]	[-3.60, -0.04]
p-value	0.0014	0.0450
Week 12 **MGC**, n	89	91
LS mean (SE)	-7.56 (1.39)	-9.34 (1.02)
95% CI	[-10.31, -4.81]	[-11.36, -7.32]
Week E12, n	68	69
LS mean (SE)	-12.57 (1.70)	-11.92 (1.02)
95% CI	[-15.94, -9.20]	[-13.94, -9.89]
Difference between Week E12 versus parent study Week 12	-5.01	-2.58
95% CI	[-10.07, 0.05]	[-5.21, 0.06]
p-value	0.0525	0.0550
Week 12 **MG-QOL15r**, n	88	90
LS mean (SE)	-2.36 (1.12)	-5.72 (1.10)
95% CI	[-4.56, -0.15]	[-7.89, -3.54]
Week E12, n	68	68
LS mean (SE)	-8.52 (1.64)	-9.06 (1.12)
95% CI	[-11.76, -5.27]	[-11.28, -6.84]
Difference between Week E12 versus parent study Week 12	-6.16	-3.35
95% CI	[-10.13, -2.19]	[-5.67, -1.02]
p-value	0.0027	0.0053

In the ZLP 0.3/ZLP 0.3mg/kg treatment group and the PB/ZLP 0.3mg/kg treatment group, 4 study participants (4.3%) and 3 study participants (3.3%), respectively, received rescue therapy from MG0011 Baseline through Week E12.

Subgroup analyses

Table 29: Subgroup analysis of change from MG0011 baseline to week E12 in MG-ADL. QMG, MGC and MG-QOL15r (mITT Population)

Subgroup Category	**Placebo/ ZLP 0.3mg/kg N=90**		**ZLP 0.3/ 0.3mg/kg N=92**	
	N	**Mean CfB (SD)**	**n**	**Mean CfB (SD)**
Overall **MG-ADL** CFB at Week E12	69	-3.19 (3.86)	71	-1.20 (2.90)
Age				
<65 years	47	-3.57 (4.31)	54	-1.15 (3.25)
≥65 years	22	-2.36 (2.56)	17	-1.35 (1.37)
Baseline MG-ADL				
≤9	46	-1.76 (2.39)	59	-0.56 (2.16)
≥10	23	-6.04 (4.66)	12	-4.33 (4.01)
Baseline QMG				
≤17	49	-2.43 (2.67)	56	-0.50 (2.15)
≥18	20	-5.05 (5.50)	15	-3.80 (3.84)
Overall **QMG** CFB at Week E12	68	-3.74 (4.86)	69	-1.65 (3.33)
Age				
<65 years	46	-4.24 (5.30)	53	-1.51 (3.50)
≥65 years	22	-2.68 (3.68)	16	-2.13 (2.75)
Baseline MG-ADL				
≤9	45	-2.80 (3.06)	58	-1.34 (3.32)
≥10	23	-5.57 (6.92)	11	-3.27 (3.04)
Baseline QMG				
≤17	48	-2.69 (3.20)	56	-1.07 (3.06)
≥18	20	-6.25 (6.97)	13	-4.15 (3.41)
Overall **MGC** CFB at Week E12	68	-5.71 (7.27)	69	-2.78 (5.29)
Age				
<65 years	46	-6.63 (8.04)	53	-2.62 (5.51)
≥65 years	22	-3.77 (4.93)	16	-3.31 (4.60)
Baseline MG-ADL				
≤9	45	-3.47 (4.19)	58	-2.10 (4.95)
≥10	23	-10.09 (9.77)	11	-6.36 (5.80)
Baseline QMG				
≤17	48	-4.25 (4.86)	56	-1.64 (4.48)
≥18	20	-9.20 (10.48)	13	-7.69 (5.88)
Overall **MG-QOL15r** CFB at Week E12	68	-4.96 (6.25)	68	-2.63 (6.13)
Age				

<65 years	46	-6.11 (6.82)	52	-2.77 (6.55)
≥65 years	22	-2.55 (4.02)	16	-2.19 (4.68)
Baseline MG-ADL				
≤9	45	-3.76 (4.74)	57	-1.74 (5.06)
≥10	23	-7.30 (8.09)	11	-7.27 (8.97)
Baseline QMG				
≤17	48	-4.38 (5.69)	55	-1.82 (5.32)
≥18	20	-6.35 (7.41)	13	-6.08 (8.16)

2.6.6. Discussion on clinical efficacy

Efficacy at 12 weeks in the main study MG0010

Study participants

Study MG0010, the single pivotal phase 3 study, was a randomised double-blind placebo-controlled study comparing the efficacy of ZLP 0.3mg/kg with placebo. Patients included were to be Acetylcholine-receptor antibody positive, MGFA class II-IV, have at least an MG-ADL score of 6 and a QMG score of at least 12 with a score of at least 2 in at least 4 items. The requirements of the disease manifestations are strict and decreases the proportion of patients with mild disease. This can be seen in the baseline disease characteristics where more than 70% of participants had at least moderate weakness according to the MGFA classification, mean MG-ADL was 10.6 and mean QMG was 19.1.

For comparison, the baseline QMG ranged between 8.5 and 19.4 in the 27 MG studies analysed in the systematic literature report submitted by the applicant. The highest QMG score (19.4) was reported in a study by Liu et al (2010) and in the PB group of Study MG0010. The cohort of patients selected from the MG-registry for the external reference of study MG0011 (requirement of baseline MG-ADL≥6), had a baseline QMG of 12.9 and baseline MG-ADL 7.4 before using Odds Weighting. The two cohorts from the MGTX study included in the modelling for the reference group, had an index mean QMG of 13.7 and mean MG-ADL of 8.0 before using Odds Weighting.

Patients with MGFA class V were excluded.

Sample size

The initially planned enrolment was approximately 130 subjects (65 subjects per arm) assuming a difference between treatment arm in CBL in MG-ADL score week 12 of 2.3. With global amendment 1 (CSP version 2.0, 18 December 2020) the total sample size was increased to account for a higher variability (standard deviation 3.7) in the primary endpoint than what had originally been assumed (3.4). The new sample size calculation implied a total sample size of 156 subjects (78 per treatment arm). No update or sample size re estimation (blinded or unblinded) had been pre-planned and no further details had been found shedding any light on what caused variability considerations. The Applicant clarified that no data from the study will have been used or known. Instead, the applicant will have conducted a literature review. The reason appears to have been a sanity check after the Ra Pharma acquisition.

Subjects who prematurely discontinued participation prior to the Day 84 visit may have been replaced. A similar approach was planned in the phase 2 study MG0009 (see below) and is not endorsed. Contrary phase 2 sample size, the study MG0010 sample size will have been accounted for not only an assumed dropout rate but also that approximately 5% of subjects were expected to use rescue. Details were lacking, and the applicant was requested to clarify whereafter the applicant confirmed that replacement

had been allowed as per study MG0010 protocol but that no replacement of discontinued study participants occurred.

In the end, more subjects (N=174) than planned within amendment 1 (N=156) were randomised into the study. Contrary to the applicant's statement in connection with the same "issue" in the phase 2 study, no explanation had been offered for the phase 3 study. As was clarified by the applicant, this will have been due to the many sites recruiting patients, the safety margin applied before closure of screening to ensure the randomisation of at least 156 participants and, in the end, a slightly lower screen failure rate than initially expected.

Randomisation and masking/blinding

Except for what currently appears to have been a protocol-defined opportunity to replace randomised subjects dropping out early, the randomisation procedure seems to have been appropriate. Randomisation was performed using a 1:1 allocation ratio and subjects were stratified based on baseline MG-ADL Score (≤9 versus ≥10), QMG Score (≤17 versus ≥18), and geographical region (North America, Europe, and Japan).

Study MG0010 was to be performed under double-blind conditions. Subjects and study staff was to remain blinded to treatment assignments until after database lock and unblinding of data. Dosing was weight-based and according to the SmPC, there are three zilucoplan presentations implying pre-filled syringes of 0.416 mL, 0.574 mL, and 0.810 mL each containing a different amount of zilucoplan sodium. Matching placebo for the 0.3 mg/kg dose was to be provided in one presentation (0.574 mL). However, it had not been confirmed that active treatment was also to be provided in one presentation of 0.574 mL or if not, what other means were in place to achieve masking of treatments, e.g., whether the pre-filled syringes were in any way covered. Considering that primary and secondary endpoints relied on patient and physician reported outcomes success in concealment of treatment assignment is vital and the applicant was requested to clarify. The initially missing piece of information will have been that to blind study participants and site personnel to the small differences in volumes/plunger positions, safety syringes were wrapped with a label which fully masked the prefilled syringe cartridge. Few subjects discontinued the study (<5%) and not that many subjects needed rescue therapy although more subjects in the placebo group than in the zilucoplan group. This could be considered as one piece of evidence that masking of treatments was successful and maintained throughout the double-blind study period.

Statistical analysis plan

Zilucoplan was initially developed by Ra Pharmaceuticals, Inc. (Ra Pharma), which was acquired by UCB on 02 Apr 2020. This may explain some of the changes introduced with the CSP version 2 as well as the changes made to the original SAP (approved 6 Nov 2019). There was one global amendment to the CSP forming protocol version 2.0 which led to SAP amendment 1 (01 Feb 2021). In total, there have been five amendments to the SAP, all of which have been submitted including a revision history. The last SAP version (version 5.0) was dated 06 Dec 2021.

For the definition of the primary estimand, three ICE had been identified all of which initially were to be considered using a hypothetical strategy. With SAP amendment 4 (dated 13 Oct 2021), the primary estimand was revised, and the definition of ICE was slightly amended (based on regulatory feedback (FDA)). Also, the strategy changed such as rescue therapy (ICE1), death and MG crisis (ICE2) were to be seen as treatment failures. This could be agreed. Study discontinuation for reasons other than death or a MG crisis (ICE3), was to be handled applying a hypothetical strategy which is considered aligned with the statistical analysis model based on an MMRM ANCOVA and for which monotone missing after ICE3 was considered MAR. This is seldom an appropriate assumption and concerned here for example study discontinuations due to an adverse event (AE).

The approach to handle missing or censored data in case of rescue, death or an MG crisis was imputation of baseline or last available assessment (including unscheduled visits) whichever was worst.

The number of subjects with an ICE was 11/88 (12.5%) in the placebo arm and 6/86 (7.0%) in the zilucoplan arm. The most common ICE was use of rescue therapy concerning 10/11 subjects (placebo) and 4/6 subjects (zilucoplan) with an ICE. One subject in each arm died. Two subjects in the zilucoplan arm, none in the placebo arm, discontinued the study due to an AE. According to the presentation of ICEs, it was only one subject (zilucoplan) who experienced an event falling into the category ICE3.

In each treatment arm it was less than 5% of the subjects who did not complete the study: 4/88 (4.5%): placebo and 4/86 (4.7%): zilucoplan. The number of subjects with intermittently missing MG-ADL total scores (not attributed to an ICE) differed slightly across visits and comparing treatments but raise no major concern.

The primary efficacy analysis set was the mITT. The intention excluding subjects who did not receive any treatment or who did not provide any postbaseline efficacy assessment is not supported but since all randomised subjects were included in the mITT there is no need to pursue this further.

Besides the primary estimand, several supplementary and sensitivity analyses had been planned. Not all are agreed as sufficiently challenging but can be agreed to represent slightly different assumptions. Among the latter was the primary analysis repeated using J2R: among the former a treatment policy estimand where all data were to be used regardless of any ICE (i.e., data after rescue use was not censored). Both are appreciated and both showed outcomes not that dissimilar compared with the primary endpoint primary analysis. Estimated treatment differences were slightly smaller but (still) statistically significant. However, in the treatment policy analysis, any missing MG-ADL score was to be handled assuming MAR. It may be that not that many had missing scores week 12 but an additional treatment policy analysis without relying only on the MAR assumption was requested. This analysis (using J2R and assuming missing not at random) confirmed the outcome of the primary analysis of the primary endpoint.

In addition, the applicant has confirmed that none of the study participants in the mITT population who received rescue therapy discontinued the study; therefore, all were followed after initiation of rescue therapy.

Within SAP amendment 3 (17 June 2021) the multiplicity strategy for secondary endpoints was modified justified by the small number of events expected for the secondary endpoints in the lowest part of the hierarchy. The revision of the multiple testing procedure (MTP) implied the implementation of two families of secondary endpoints where endpoint 1-3 with order of appearance kept, formed family 1 defined as key secondary endpoints that was to be tested in a fixed sequential order. Secondary efficacy endpoints 4-7 was then to form family 2 with multiplicity to be controlled with Holm's procedure using a gatekeeping approach. The modified version of the MTP is per se not objected to but since changed rather late into the study, and since it implied that not all of the secondary endpoints defined as forming family 2 failed, as will have been the case had the original version been kept, and since study MG0010 serves as the only confirmatory study submitted, the applicant was requested to provide more details on the process and what triggered the considerations leading to the modification of the testing strategy. During the procedure, not much new information was provided. The applicant claimed that for Family 2, including the last 4 secondary endpoints of the testing strategy (i.e., time to rescue therapy, achieving MSE (minimal symptom expression), MG-ADL response without rescue therapy, QMG response without rescue therapy), there was less clinical rationale to justify the hierarchy. In addition, as described also in the SAP, only a small number of events were expected for the secondary endpoints forming Family 2. The reasons are per se undisputable. The Ra Pharma acquisition is mentioned, however, if the change in the MTP was to pass as part of a sanity check of the SAP, it could have been expected to have been

implemented earlier. However, no new concern has been raised. Importantly, and as also pointed out by the applicant, the revised MTP was implemented 7 months prior to unblinding.

The primary analysis of the study was performed when all subjects had completed the double-blind 12-week treatment period. Database lock occurred on 18 Jan 2022.

Primary efficacy endpoint

The effect of ZLP 0.3 mg/kg started early as measured with CBL in MG-ADL. A numerical difference between the placebo group and the ZLP group was seen already at week 1. The effect of PB and of ZLP stabilised after approximately four weeks with a steady difference up to week 12 at primary endpoint assessment. A statistically significant difference to PB in CBL of – 2.09 ($p<0.001$) was found. All sensitivity analyses showed highly significant treatment difference between PB and ZLP of slightly more than 2 points, which has been found clinically relevant (Muppidi et al, Muscle Nerve 44: 727–731, 2011).

Secondary efficacy endpoints

As the primary efficacy endpoint, CBL in MG-ADL, is a score based on subjective change according to the study participant, the first secondary endpoint, CBL in QMG, is important as it is the result of a physical examination under controlled circumstances. What can be regarded as a clinically relevant change in QMG has been stated in the literature. Bahron et al 1998 found that a treatment must produce more than 2.6 units of QMG change to be of clinical significance. QMG score changes of up to 2.6 units are expected to occur due to variability of repeated observations. Katzberg et al 2014 concluded that the minimal clinically important difference depends on baseline QMG and if QMG>16, the minimal clinically important difference should be -2.75. According to MGFA, recent data support the use of a 2- or 3- point of change in QMG as a criterion for minimal clinically significant change and depending on MG severity; in mild (QMG 0-9) to moderate disease (QMG 10-16), a 2-point change is clinically significant and a 3-point change is significant for severe MG (QMG >16) (https://myasthenia.org/Professionals/Resources-for-Professionals Jan 8, 2023). The result of Study MG0010 with a CBL and compared to PB of -2.94 ($p<0.001$), can thus be regarded as clinically relevant in the studied population.

The secondary efficacy endpoints MGC and MG-QOL15r further support the efficacy of ZLP with statistically significant results at 12 weeks in the studied population with CFB of -3.20 and -2.49 respectively.

The maximal improvement was obtained during the first 4 to 8 weeks of treatment. However, a substantial number of study participants requires longer durations of treatment to respond, and it is therefore not possible to recommend a specific time period at which discontinuation of treatment should be considered in case of no or weak response to treatment.

Supportive data from Study MG0009, efficacy at week 12

The phase II 12-week randomised DB placebo-controlled dose-finding study MG0009 investigated two ZLP dose levels (0.1 mg/kg and 0.3 mg/kg). Inclusion and exclusion criteria were similar to the phase III trial MG0010 and the included participants had similar baseline characteristics. Efficacy endpoints were assessed as CFB at 12 weeks with QMG as the primary endpoint. The sample size was very limited: based on the assumptions made, 12 subjects per arm were required and subjects who discontinued prior to the day 84 visit could be replaced. In the end, 45 instead of 36 subjects were randomised and according to the applicant the reason for this was 2-fold whereof one of the explanations will have been the fact that subjects could be replaced. This is not endorsed. Upon request, the applicant confirmed that although replacement was allowed per the study protocol, no replacement of discontinued study participants occurred. Blinding of randomised treatment was to be achieved using matching placebo. However, it remained to be confirmed that prefilled syringes matched irrespective of active dose-level

or placebo. What appears to initially have been the missing piece of information was that to blind study participants and site personnel to the small differences in volumes/plunger positions, safety syringes were wrapped with a label which fully masked the prefilled syringe cartridge.

The primary analysis of the primary endpoint was the comparison between the 0.3 mg/kg zilucoplan group and the placebo group: the comparison versus the lower dose (0.1 mg/kg) and placebo was described as a secondary endpoint. There were no formal multiplicity considerations. In case of data missing last-observation-carried-forward was used. Testing was planned and performed using a one-sided 0.10 significance level and outcomes were presented with two-sided 80% CIs.

For the primary and important secondary endpoints, 95% CIs was requested. The applicant provided new estimates and as could be expected, all 95% CIs included 0.

CBL in in the ZLP 0.3 mg/kg compared to placebo after 12 weeks was MG-ADL -2.3 (95% CI: -4.9, 0.3) , QMG -2.8 (95% CI: -6.3, 0.6), MGC -4.1 (95% CI: -8.6, 0.5) and MG-QOL15r -3.7 (95% CI: -8.6, 1.1). Despite a lack of scientific stringency, these results may lend some support to the findings of MG0010.

Supportive data from Study MG0011, efficacy at week 12

Study MG0011 was an open label phase III study which included participants who had completed either of studies MG0009 or MG0010. As there is no PB control and participants knew that they received ZLP 0.3mg/kg, efficacy data cannot be directly compared to the other results but contribute with some information of interest. With conservative imputation participants who received ZLP in study MG0011 but had received PB in parent study MG0010, decreased their LSM MG-ADL score with 2.87 points after 12 weeks of ZLP treatment. In study MG0010 (ZLP treated participants) the CBL not corrected for the PB effect was -4.68. Corresponding data for QMG were MG0011 –3.77 and MG0010 -6.48, MCG MG0011 –5.56 and MG0010 -8.85, MG-QOL15r MG0011 -4.54 and MG0010 -6.21. These 12-week data support the findings of study MG0010.

Main efficacy issues

Study population

Inclusion criteria of studies MG009 and MG0010 for baseline disease severity were partly the same as in the studies of other recently approved products in gMG for MGFA (class II-IV) and MG-ADL (≥6), but the ZLP studies had two additional requirements: QMG ≥12 and at least a score of 2 in at least 4 items. These distort the study population towards the moderate-severe part of the disease severity distribution. Enrichment of patients displaying more signs and symptoms in order to increase the range of possible improvement in a clinical trial, may be acceptable. In the pivotal MG0010 a patient population with more disease manifestations than usually seen in gMG under standard of care has been enriched and patients with mild disease based on QMG, has not been included. This can be seen when comparing to baseline data of other clinical trials in the literature (please see above). Compared to recently approved medicinal products in gMG, the population in MG0010 is most similar to the one used in the pivotal trial of eculizumab (EMA/410939/2017). Mean baseline QMG in study MG0010 is higher than in the pivotal trials of ravulizumab and efgartigimod (19.1, compared to 14.6 and 15.9, respectively) (EMA/686052/202, EMA/641081/2022).

In subgroup analyses of study MG0010, which should be interpreted with caution, there was a pattern of smaller magnitude of efficacy in participants with a milder disease. This pattern was also seen in the OL Study MG0011, with the largest difference between patients with mild and moderate-severe disease in participants assessed after the longer treatment duration of 24 weeks. *Post hoc* subgroup analyses used data imputation (scores after rescue therapy or any death or myasthenic crisis were imputed based on baseline score or on the last available score, whichever was worst, other missing scores, including

discontinuation, were handled under the MAR assumption) in contrast to the original subgroup analyses. In explored subgroups (based on MG-ADL at baseline, QMG at baseline and MGFA at baseline), no clear correlation was observed between the effect size (CBL, responder rate) of zilucoplan and disease severity. Efficacy can be extrapolated to patients not included in the pivotal study population (QMG <12, still symptomatic despite standard of care), as it is considered that efficacy can be extrapolated based on the mechanism of action with reduced complement dependent cytotoxicity. This indication is also in line with of other authorised gMG products.

Study duration

The DB phase of studies MG0009 and MG0010 was 12 weeks. Pivotal trials in gMG for other products, including products with similar mechanism of action, have all used at least 24 weeks for the controlled phase followed by an OL. This was also the advice given by the CHMP (EMEA/H/SA/3949/2/2019/SME/III) and the recommendation to include a 24-weeks double-blind placebo-controlled period in the pivotal trial in order to demonstrate maintenance of effect and long-term safety, was reiterated in the follow up advice EMEA/H/SA/3949/2/2019/SME/III. In a national scientific advice meeting with the Swedish Medicinal Products Agency in November 2021, it was acknowledged that while there are no FDA nor EMA regulatory guidelines for drugs in the development for gMG, there is precedence of approved drugs with a study duration longer than 12 weeks. Longer studies can be conducted without ethical issue as patients in the placebo (PB) group are receiving standard of care and it appears there are a sufficient number of patients to be included in a 24-week study. MPA raised the question if a 12-week study would be of sufficient duration, given that myasthenia gravis fluctuates over time and that a sufficient number of measurements of primary and secondary endpoints of MG-ADL and QMG will be needed to capture a difference over time vs placebo.

24 weeks and 60 weeks efficacy data MG0011

Participants who were treated with ZLP for 24 weeks improved their MG-ADL from the original baseline to week E12 and numerically from week 12 to week E12. The MG-ADL change between MG0010 baseline and week E12 (i.e. 24 weeks) with conservative imputation was -5.33 which is slightly larger than the result at week 12 (i.e. 12 weeks), -4.68, implying a difference of -0.65 points. Secondary endpoints QMG, MGC and MG-QOL15r, all showed numerically slight improvement at 24 weeks, difference between week 12 and week E12 being -0.62, -1.06 and -1.85 respectively. These data together with analyses of other factors contributing to efficacy estimates, may support 24 weeks efficacy. However, longer-term treatment with ZLP is anticipated and the applicant was requested to provide more data. To support long-term efficacy, a more recent snapshot of MG0011 was taken on 11 May 2023 and descriptive analyses restricted to study participants coming from MG0010 were performed. As of the new snapshot, 85.5% (142/166) of former MG0010 study subjects had completed 48 weeks of active treatment and 18.1% (30/166) of the subjects had used rescue therapy in MG0011. Analyses based on observed data showed an increase in CBL comparing data from week 12 and week 48 interpreted as to probably be due to responders remaining on trial. In an analysis in which subjects who discontinued the study or used rescue therapy were counted as treatment failures and subjects who died were assigned the worst possible score from the time of death, similar results weeks 12 and 48 were obtained. Together, these data suggest sustained efficacy at a clinically relevant magnitude over time.

24 weeks efficacy data Extension portion of study MG0009

Participants who completed the main portion of MG0009 could enter the OLE portion. The first 24 weeks of active treatment include data at week 12 of the Extension portion of participants treated with ZLP in the Main portion, and data at week 24 of the Extension portion of participants treated with PB in the main portion. Thus, all participants analysed had the same duration (24 weeks) of active treatment. QMG CBL at week 24 was numerically larger, -7.50 than at 12 weeks (-6.0). Secondary endpoints (MG-ADL, MGC and MG-QOL15r) all showed numerically similar, or slightly larger improvement at 24 weeks.

Model informed analysis

To overcome the lack of PB control the last 12 weeks (i e the 12 weeks of the MG0011 OL study), the applicant tried to obtain a reference of what CBL can be expected in patients treated with standard of care (the treatment given the PB participants in studies MG0009 and MG0010) for 24 weeks. The applicant made substantial effort to find appropriate and representative subjects with similar disease and patient characteristics as those included in studied MG0009 and MG0010. These external, historical data included group-level data from a systematic literature review (SLR, 6 studies with approx. 312 placebo patients) and patient-level data from the Swedish MG-Registry (Cohort 1A: 16 patients) and the MGTX trial (SOCb and T+SOC: 53 patients). The performed primary analysis was considered appropriate and the performed Bayesian analysis in terms of statistical modelling and model diagnostics are supported. Considering the multiple options of modelling decisions required in these complex analyses, the efforts of the applicant to be transparent and pre-specify the statistical methods is acknowledged.

The major issues of the presented results include the potential for different kinds of bias. The applicant addressed these issues by providing comprehensive sensitivity, supplemental and secondary analyses. Although these additional analyses were consistent with and, therefore, support the primary results, it is unclear to what degree potential residual bias from unmeasured or unknown confounders or deviations from model assumptions remains. Therefore, the provided evidence is in principle considered inferior relative to a corresponding double-blinded, randomised controlled study.

This means, while the arguments for a non-random (cf. statistically significant), clinically relevant difference between the treated groups at week 24 seem convincing, the causal inference explaining the observed differences between groups exclusively as a treatment effect is less so.

Predicted efficacy (CBL MG-ADL) at week 24 was -4.66. In study 0011, the MG-ADL CBL at week 24 was -6.30. Predicted PB CBL was -2.06. As the efficacy magnitude was not predicted correctly, this casts doubt on the modelled analysis and the reliability of the predicted PB effect and the PB free efficacy magnitude of MG-ADL CBL.

The mechanism of action and the known long-term efficacy of products approved in gMG with similar mechanism of action (C5 inhibitors eculizumab and ravulizumab), may increase the probability of maintained efficacy with ZLP treatment. The applicant has provided further analyses and a discussion including justification why it could be expected that the efficacy of ZLP will be maintained at a clinically relevant magnitude during 60 weeks of treatment. Potential sources of error such as responders remaining on trial, use of rescue treatment and prohibited medications, placebo effect and spontaneous disease fluctuations were discussed and it can be concluded that there is effect of ZLP at 60 weeks, even if the treatment efficacy cannot be isolated, and the true treatment efficacy cannot be separated from e.g., subject-expectancy effect or spontaneous disease fluctuations.

Age and age at disease onset

In study MG0011, at 12 weeks, there is a numerical difference with smaller efficacy magnitude in participants ≥65 years of age in the former PB participants. The difference is minor in the MG-ADL score, but quite evident in the secondary efficacy endpoints. In Study MG0010, elderly participants seemed to benefit less than younger only when looking at the quality-of-life score, MG-QOL15, where the elderly participants even improved more in the PB group than the ZLP group (with 1.34 points) while the younger participants treated with ZLP improved more compared to PB with 3.37 points. To understand this better, analyses based on age at disease onset were performed. Lately, the division info three subgroups based on age at onset has shown purposeful, early <50, late ≥50 to <65 years, very late ≥65 years) (Cortés-Vicente et al, 2020). Efficacy analyses with conservative imputation show that participants with very late onset display a large placebo effect as measured with MG-ADL and QMG. This may be due to regression to the mean in a study of patients with a fluctuating disease and strict inclusion criteria (Benatar *et al*

2012). Subgroup analyses should always be interpreted with caution, some variability and findings by chance are expected in case of multiple analyses. Efficacy resulting from inhibition of CDC in AchR antibody mediated disease, should however be the same regardless of age or age at onset. Most data point to a fair effect in elderly patients and in patients with late and very late onset of disease and a restriction to the indication is not justified.

The estimated efficacy in participants who at baseline were classified as treatment refractory, was numerically larger than in participants not classified as refractory. This may partly be due to confounding; there may be a correlation between severe disease manifestation and being treatment refractory, and between severe disease manifestation and larger efficacy magnitude. Nevertheless, treatment refractory participants seem to benefit to a relevant extent from ZLP treatment.

2.6.7. Conclusions on the clinical efficacy

Efficacy of ZLP 0.3 mg/kg in the treatment of gMG in the studied patient population is clinically relevant and statistically highly significant at 12 weeks. The primary efficacy endpoint of the pivotal study is supported by results from studies MG0009 and MG0011, sensitivity analyses, secondary efficacy endpoints, pharmacodynamic studies and mechanism of action. Thus, the efficacy at 12 weeks in the studied population can be regarded as robust and compelling.

Analyses on the open label data from study MG0011 including analyses of responders remaining in the trial, placebo effect, effect due to expectations and disease fluctuations, have been sufficiently reported and the results may support efficacy for 24 weeks. Based on a new, a more recent snapshot of MG0011 (11 May 2023) and additional analyses restricted to subjects coming from MG0010, also longer term efficacy can be considered supported in that these data suggest sustained efficacy at a clinically relevant magnitude over time. As of the new snapshot, 85.5% (142/166) of former MG0010 study subjects had completed 48 weeks of active treatment.

Subgroup analyses on efficacy in patients included in MG0010 and MG0011 show similar efficacy in participants with milder and more severe disease, indicating that the efficacy may be sufficient in patients with even milder disease manifestations. The indication is not restricted to the pivotal study population, who had QMG ≥12 and at least four QMG items of at least score 2. The CHMP considers that efficacy can be extrapolated to patients with less severe disease but who are still symptomatic despite standard of care, based on mechanism of action with reduced complement dependent cytotoxicity, and safety profile is likely similar.

2.6.8. Clinical safety

2.6.8.1. Introduction

The evaluation of the safety of zilucoplan in the treatment of patients with gMG is based on data from the 3 studies included in this application.

In addition, zilucoplan has been investigated for use in immune mediated necrotizing myopathy (IMNM) and several other diseases, of which the similar disease characteristics of IMNM allowed for pooling of safety data with the phase 2 study from this development programme to enlarge the safety pool.

2.6.8.2. Patient exposure

Exposure and patient populations studied

A total of 213 study participants with gMG, have received zilucoplan in the clinical development programme as of the clinical cutoff date 18 Feb 2022, including 212 study participants at the proposed therapeutic dose of 0.3mg/kg. A total of 138 gMG study participants were exposed at least 6 months (137 study participants at 0.3mg/kg dose) and 91 gMG study participants exposed for more than a year (87 study participants at 0.3mg/kg dose). A total of 154 study participants have been exposed to ZLP for more than a year in any indication (gMG, IMNM, paroxysmal nocturnal haemoglobinuria [PNH], and amyotrophic lateral sclerosis [ALS]) including 150 study participants at the 0.3mg/kg dose level.

The safety evaluation for ZLP primarily utilised 4 pools:

- Pool S1A: 12-week placebo-controlled safety pool including data from the Phase 2 and Phase 3 study in gMG (115 study participants in the ZLP 0.1mg/kg+0.3mg/kg group with 26.4 participant-years at risk).
- Pool S2A: 8/12-week placebo-controlled safety pool including data from the Phase 2 and Phase 3 study in gMG and the Phase 2 study in IMNM (127 study participants in the ZLP 0.1mg/kg+0.3mg/kg group with 28.3 participant-years at risk).
- Pool S1B: long-term safety pool with data on all ZLP-exposed participants in gMG, from the placebo-controlled Phase 2 and Phase 3 study in gMG and their OLE studies (213 study participants in the All ZLP group with 262.4 participant-years at risk).
- Pool S2B: long-term safety pool with data on all ZLP-exposed participants in gMG and IMNM, from the placebo-controlled Phase 2 and Phase 3 studies in gMG and their OLE studies (238 study participants in the All ZLP group with 275.2 participant-years at risk).

The pools including only gMG study participants (Pool S1A and S1B) are considered the primary pools for analysis unless otherwise stated.

The number of study participants in the ZLP 0.1mg/kg treatment group was limited compared with the number of study participants in the placebo and ZLP 0.3mg/kg treatment groups in the pooled analyses. For the gMG studies, the ZLP 0.1mg/kg dose was only used in the Phase 2 study (MG0009).

Demographics

For Pool S1B, the mean (SD) age of study participants at first study entry was 52.4 years (15.3), with most of the study participants (74.2%) in the age category 18 to <65 years of age. The majority of study participants were female (55.4%) and white (74.6%). The mean body weight and mean body mass index (BMI) were 90.50kg and 31.3kg/m^2.

Table 30: IMP duration and participant years of time at risk for pool S1A and pool S1B

	Pool S1A (placebo-controlled period, gMG studies)				**Pool S1B (long-term, gMG studies including open-label)**		
	Placebo N=103	**ZLP 0.1mg/kg N=15**	**ZLP 0.3mg/kg N=100**	**ZLP 0.1mg/kg+ 0.3mg/kg N=115**	**ZLP 0.1mg/kg N=22**	**ZLP 0.3mg/kg N=212**	**All ZLP N=213**
IMP duration (days)							
n	103	15	100	115	22	212	213
Mean (SD)	81.7 (12.2)	82.8 (2.3)	82.0 (10.6)	82.1 (9.4)	357.8 (88.4)	406.6 (360.6)	441.7 (412.0)
Median	84.0	84.0	84.0	84.0	388.5	280.5	288.0
Min, max	1, 96	77, 87	15, 94	15, 94	104, 476	14, 1517	14, 1517
Duration of IMP							
≥1 day n (%)	103 (100)	15 (100)	100 (100)	115 (100)	22 (100)	212 (100)	213 (100)
≥30 days n (%)	101 (98.1)	15 (100)	98 (98.0)	113 (98.3)	22 (100)	205 (96.7)	207 (97.2)
≥60 days n (%)	99 (96.1)	15 (100)	96 (96.0)	111 (96.5)	22 (100)	187 (88.2)	189 (88.7)
≥90 days n (%)	4 (3.9)	0	5 (5.0)	5 (4.3)	22 (100)	180 (84.9)	182 (85.4)
≥6 months n (%)	-	-	-	-	21 (95.5)	137 (64.6)	138 (64.8)
≥12 months n (%)	-	-	-	-	12 (54.5)	87 (41.0)	91 (42.7)
≥18 months n (%)	-	-	-	-	0	55 (25.9)	57 (26.8)
≥24 months n (%)	-	-	-	-	0	38 (17.9)	39 (18.3)
≥36 months n (%)	-	-	-	-	0	15 (7.1)	31 (14.6)
≥48 months n (%)	-	-	-	-	0	1 (0.5)	1 (0.5)
Total IMP duration (participant-years)	23.0	3.4	22.4	25.8	21.6	236.0	257.6
Total time at risk (participant-years)	23.4	3.4	23.0	26.4	21.6	240.7	262.4

gMG=generalised myasthenia gravis; IMP=investigational medicinal product; ISS=Integrated Summary of Safety; max=maximum; min=minimum; SD=standard deviation; ZLP=zilucoplan
Note: IMP duration is defined as (Date of Last Dose - Date of First Dose + 1)
Note: Time at risk is defined as the exposure duration (Date of End of Observation Period - Date of First Dose + 1) where the observation period includes the time up to the Safety Follow-up Visit or 40 days after the final dose, whichever is earliest.

Note: As participants may have received more than 1 ZLP dose level, the All ZLP column is not a total of the previous dose columns.

Table 31: Cumulative duration of exposure (pool S2B)

Duration of exposure	All Zilucoplan N=238 n (%)	Subject -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

Note subject-years of exposure duration is defined as (date of end of observation period – date of first dose +1) where the observation period includes the time up to the safety follow-up visit or 40 days after the last dose, whichever is earliest

2.6.8.3. Adverse events

Differences in incidences between treatment groups are assessed as per the following criteria: similarity is stated for incidences varying by <2.5%; a slight difference in incidence is stated for variations of ≥ 2.5% to <5%; and differences are stated from ≥5% onwards.

Table 32: Incidence of TEAEs – Overview (Pool S1A)

Category	**Placebo N=103 n (%)[#]**	**ZLP 0.1mg/kg N=15 n (%)[#]**	**ZLP 0.3mg/kg N=100 n (%)[#]**	**ZLP 0.1mg/kg+0.3mg/kg N=115 n (%)[#]**
Any TEAEs	76 (73.8) [275]	15 (100) [58]	78 (78.0) [351]	93 (80.9) [409]
Serious TEAEs	16 (15.5) [18]	0	16 (16.0) [21]	16 (13.9) [21]
Study participant. discontinuations due to TEAEs	2 (1.9) [2]	0	4 (4.0) [4]	4 (3.5) [4]
Treatment-related TEAEs	27 (26.2) [40]	8 (53.3) [22]	32 (32.0) [60]	40 (34.8) [82]
Severe TEAEs	14 (13.6) [17]	2 (13.3) [3]	14 (14.0) [30]	16 (13.9) [33]
Deaths (TEAEs leading to death)	1 (1.0) [1]	0	1 (1.0) [2]	1 (0.9) [2]

AE=adverse event; ISS=Integrated Summary of Safety; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Treatment-related TEAEs are those defined as related by the Investigator.
Note: There were no additional nontreatment-emergent AEs leading to death.

Table 33: Incidence of common TEAEs reported in ≥5% of study participants by PT (Pool S1A)

MedDRA v24.0 SOC PT	Placebo N=103 n (%)	ZLP 0.1mg/kg N=15 n (%)	ZLP 0.3mg/kg N=100 n (%)	ZLP 0.1mg/kg+0.3mg/kg N=115 n (%)
Gastrointestinal disorders				
Diarrhoea	3 (2.9)	1 (6.7)	10 (10.0)	11 (9.6)
Nausea	1 (1.0)	2 (13.3)	4 (4.0)	6 (5.2)
General disorders and administration site conditions				
Injection site bruising	10 (9.7)	2 (13.3)	14 (14.0)	16 (13.9)
Injection site pain	4 (3.9)	0	8 (8.0)	8 (7.0)
Oedema peripheral	1 (1.0)	0	5 (5.0)	5 (4.3)
Infections and infestations				
Nasopharyngitis	3 (2.9)	1 (6.7)	5 (5.0)	6 (5.2)
Urinary tract infection	4 (3.9)	1 (6.7)	7 (7.0)	8 (7.0)
Injury, poisoning and procedural complications				
Contusion	4 (3.9)	1 (6.7)	8 (8.0)	9 (7.8)
Investigations				
Amylase increased	3 (2.9)	0	7 (7.0)	7 (6.1)
Lipase increased	3 (2.9)	0	6 (6.0)	6 (5.2)
Nervous system disorders				
Headache	17 (16.5)	6 (40.0)	16 (16.0)	22 (19.1)
Myasthenia gravis	13 (12.6)	4 (26.7)	10 (10.0)	14 (12.2)

ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of participants reporting a TEAE in any study period.

The number of study participants in the ZLP 0.1mg/kg treatment group (N=15 [Pool S2A]) was limited compared with the number of study participants in the placebo (N=118 [Pool S2A]) and ZLP 0.3mg/kg (N=112 [Pool S2A]) treatment groups. Potential dose response is evaluated where possible in respective sections, but for some analyses, the numbers were too small to draw any meaningful conclusions. Overall, no dose response has been observed with respect to safety.

Adverse Drug Reactions (ARDs)

Pool S2A includes randomised placebo-controlled study data in study participants with gMG and IMNM and was selected as the main pool to suggest potential ADRs as it is the largest placebo-controlled pool with no major differences in population characteristics or exposure to the product.

The identification of undesirable effects/ADRs was based upon a best evidence assessment of all collected safety data and other relevant evidence to the assessment of causality, severity, and frequency.

Table 34: Adverse drug reactions for ZLP (incidences from Pool S2A)

MedDRA Version 24.0 SOC ADR	Placebo N=118 n (%)	ZLP N=127 n (%)	Frequency Category[a]
General disorders and administration site conditions			
Injection site reactions[b]	17 (14.4)	32 (25.2)	Very common
Infections and infestations			
Upper respiratory tract infections[c]	8 (6.8)	17 (13.4)	Very common
Gastrointestinal disorders			
Diarrhoea[d]	3 (2.5)	11 (8.7)	Common
Investigations			
Amylase increased[e]	3 (2.5)	8 (6.3)	Common
Lipase increased[f]	3 (2.5)	6 (4.7)	Common
Blood eosinophils increased[g]	0	1 (0.8)	Uncommon
Skin and subcutaneous tissue disorders			
Morphoea[h]	0	0	Common

ADR=adverse drug reaction; HLT=High Level Term; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SOC=System Organ Class, TEAE=treatment-emergent adverse event, ZLP=zilucoplan
[a] Frequency categories are based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).
[b] TEAEs in MedDRA HLT Injection site reactions
[c] TEAEs in MedDRA HLT Upper respiratory tract infections and PT Viral upper respiratory tract infection
[d] TEAEs with MedDRA PT Diarrhoea
[e] TEAEs with MedDRA PT Amylase increased
[f] TEAEs with MedDRA PT Lipase increased
[g] TEAEs with MedDRA PT Eosinophilia
[h] Morphoea was reported only in long-term open-label clinical studies. The maximum duration of exposure to ZLP during the long-term clinical studies was more than 4 years.

TEAEs by duration of treatment

In Pools S1A and S2A, the incidence of any TEAEs reported over time in the ZLP 0.1mg/kg+0.3mg/kg group were higher for the interval ≤29 days [66.1%; 66.1%] compared with ≥30 days [56.6%; 52.8%] and the same trend was observed for the placebo group. The incidence of most common AEs were similar in the ZLP 0.1mg/kg+0.3mg/kg group compared with the placebo group with the following exceptions: in the time interval ≤29 days injection site pain and diarrhoea were higher in the ZLP 0.1mg/kg+0.3mg/kg group compared with the placebo group; for the time interval of ≥30 days, amylase increased was higher and injection site bruising and headache were slightly higher in the ZLP 0.1mg/kg+0.3mg/kg group compared with the placebo group.

In Pool S1B and Pool S2B, respectively, the incidence of any TEAEs reported over time in the All ZLP group were generally similar for the time intervals up to ≤181 days (≤29 days [59.6%; 60.1%], 30 to ≤90 days [61.2%; 59.5%] and 91 to ≤181 days [59.2%; 59.5%]) with higher incidences for the longer intervals: 182 to ≤364 days [67.4%; 66.7%], ≥365 days [69.1%; 70.4%].

Overall, there was no clinically meaningful difference in incidence of TEAEs by duration of treatment.

Withdrawal effects

Overall, a review of the events of myasthenia gravis after ZLP discontinuation were not suggestive of a rebound effect. Fluctuations in symptoms are expected throughout the disease course of myasthenia gravis and were evident in both study participants with TEAEs of myasthenia gravis before and after ZLP discontinuation. No apparent withdrawal effects after cessation of treatment have been observed in any ZLP study.

2.6.8.4. Serious adverse events, deaths, and other significant events

Deaths

In the studies included in the pooled analysis, a total of 10 deaths were reported in ZLP-treated study participants, of which 1 involved a nontreatment emergent fatal AE.

In placebo-controlled periods, no imbalance was observed in the incidence of TEAEs leading to death between ZLP and placebo treatment groups (1 death occurred in each group, due to COVID-19 in the ZLP group and cerebral haemorrhage in the placebo group). Both of these deaths occurred in MG0010.

Nine deaths occurred in OLE periods (3 in MG0009, 5 in MG0011, and 1 in IMNM01), one of which involved a nontreatment-emergent fatal AE in MG0011. None of the deaths were considered treatment-related by the Investigator. An individual case review indicated that all deaths had predisposing factors and/or strong alternative explanations. Of the 5 deaths reported as cardiac arrest or with unknown cause, 1 participant experienced severe pneumonia 2 days before, 1 participant experienced bronchitis 3 days before and the cause of death could have been related to a pneumonia with sepsis, a cerebrovascular accident, or asthma attack; the nontreatment-emergent death was likely due to an underlying prostate or pancreatic carcinoma. The 2 remaining participants had major cardiovascular risk factors. The 4 other deaths were due to an accidental head injury, COVID-19 (2 study participants), and pancreatic carcinoma.

No deaths were reported in the Main portion of MG0009 or the main portion of IMNM01.

Other serious adverse events

In Pool S1A, incidences of serious TEAEs were similar in the ZLP 0.1mg/kg+0.3mg/kg group (13.9%) and in the placebo group (15.5%) (Table 35). No serious TEAEs were reported in the ZLP 0.1mg/kg group.

Table 35: Incidence of serious TEAEs by SOC and PT (Pool S1A)

MedDRA v24.0 **SOC** **PT**	**Placebo** **N=103** **n (%) [#]**	**ZLP 0.3mg/kg** **N=100** **n (%) [#]**
Any serious TEAE	16 (15.5) [18]	16 (16.0) [21]
Blood and lymphatic system disorders	0	1 (1.0) [1]
Anaemia	0	1 (1.0) [1]
Gastrointestinal disorders	1 (1.0) [1]	1 (1.0) [1]
Vomiting	1 (1.0) [1]	0
Aphthous ulcer	0	1 (1.0) [1]
General disorders and administration site conditions	0	1 (1.0) [1]
Systemic inflammatory response syndrome	0	1 (1.0) [1]
Infections and infestations	4 (3.9) [5]	6 (6.0) [9]
Abdominal abscess	0	1 (1.0) [1]
Diverticulitis	0	1 (1.0) [1]
Cellulitis	0	1 (1.0) [1]
Oesophageal candidiasis	0	1 (1.0) [1]
Oral candidiasis	0	1 (1.0) [1]
COVID-19	2 (1.9) [2]	1 (1.0) [1]
COVID-19 pneumonia	2 (1.9) [2]	1 (1.0) [1]
Herpes simplex meningoencephalitis	1 (1.0) [1]	0
Pneumonia	0	1 (1.0) [1]
Sepsis	0	1 (1.0) [1]
Investigations	0	2 (2.0) [2]
Bacterial test positive	0	1 (1.0) [1]
Lipase increased	0	1 (1.0) [1]
Musculoskeletal and connective tissue disorders	0	1 (1.0) [1]
Musculoskeletal chest pain	0	1 (1.0) [1]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (1.0) [1]
Basal cell carcinoma	0	1 (1.0) [1]
Nervous system disorders	9 (8.7) [10]	2 (2.0) [3]
Cerebral haemorrhage	1 (1.0) [1]	0
Myasthenia gravis	8 (7.8) [9]	2 (2.0) [3]
Pregnancy, puerperium, and perinatal conditions	1 (1.0) [1]	0
Hyperemesis gravidarum	1 (1.0) [1]	0
Respiratory, thoracic, and mediastinal disorders	1 (1.0) [1]	1 (1.0) [1]
Chronic obstructive pulmonary disease	1 (1.0) [1]	0

MedDRA v24.0 SOC PT	Placebo N=103 n (%) [#]	ZLP 0.3mg/kg N=100 n (%) [#]
Pulmonary embolism	0	1 (1.0) [1]

AEs of interest

Infections (non-serious)

Table 36: Incidence of nonserious infection TEAEs (Pool S2A)

MedDRA v24.0 SOC HLT PT	Placebo N=118 n (%) [#]	ZLP 0.1mg/kg+0.3mg/kg N=127 n (%) [#]
Infections and infestations	17 (14.4) [23]	33 (26.0) [40]
Abdominal and gastrointestinal infections	1 (0.8) [1]	0
Diverticulitis	1 (0.8) [1]	0
Bacterial infections NEC	0	1 (0.8) [1]
Cellulitis	0	1 (0.8) [1]
Candida infections	1 (0.8) [1]	1 (0.8) [1]
Vulvovaginal candidiasis	1 (0.8) [1]	1 (0.8) [1]
Coronavirus infections	2 (1.7) [2]	2 (1.6) [2]
COVID-19	2 (1.7) [2]	2 (1.6) [2]
Dental and oral soft tissue infections	2 (1.7) [2]	1 (0.8) [1]
Gingival abscess	0	1 (0.8) [1]
Gingivitis	1 (0.8) [1]	0
Tooth infection	1 (0.8) [1]	0
Ear infections	1 (0.8) [1]	0
Ear infection	1 (0.8) [1]	0
Escherichia infections	0	1 (0.8) [1]
Escherichia urinary tract infection	0	1 (0.8) [1]
Eye and eyelid infections	0	1 (0.8) [1]
Conjunctivitis	0	1 (0.8) [1]
Female reproductive tract infections	1 (0.8) [2]	0
Vaginal infection	1 (0.8) [2]	0
Fungal infections NEC	0	1 (0.8) [1]
Fungal skin infection	0	1 (0.8) [1]
Herpes viral infections	0	1 (0.8) [1]
Herpes zoster	0	1 (0.8) [1]
Infections NEC	0	1 (0.8) [1]

Table 36: Incidence of nonserious infection TEAEs (Pool S2A)

MedDRA v24.0 **SOC** **HLT** **PT**	**Placebo** **N=118** **n (%) [#]**	**ZLP 0.1mg/kg+0.3mg/kg** **N=127** **n (%) [#]**
Localised infection	0	1 (0.8) [1]
Influenza viral infections	0	1 (0.8) [1]
Influenza	0	1 (0.8) [1]
Lower respiratory tract and lung infections	1 (0.8) [1]	2 (1.6) [2]
Bronchitis	0	2 (1.6) [2]
Pneumonia	1 (0.8) [1]	0
Pseudomonal infections	1 (0.8) [1]	0
Urinary tract infection pseudomonal	1 (0.8) [1]	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	1 (0.8) [1]
Sepsis	0	1 (0.8) [1]
Upper respiratory tract infections	7 (5.9) [7]	16 (12.6) [16]
Nasopharyngitis	3 (2.5) [3]	7 (5.5) [7]
Sinusitis	0	5 (3.9) [5]
Upper respiratory tract infection	3 (2.5) [3]	3 (2.4) [3]
Tonsillitis	0	1 (0.8) [1]
Pharyngitis	1 (0.8) [1]	0
Urinary tract infections	4 (3.4) [4]	8 (6.3) [8]
Urinary tract infection	4 (3.4) [4]	8 (6.3) [8]
Viral infections NEC	1 (0.8) [1]	2 (1.6) [2]
Viral infection	0	1 (0.8) [1]
Viral upper respiratory tract infection	1 (0.8) [1]	1 (0.8) [1]

COVID-19=coronavirus disease 2019; HLT=High Level Term; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of participants reporting at least 1 TEAE within HLT/PT
Note: [#] is the number of individual occurrences of the TEAE

The overall incidence of nonserious infections was higher in the ZLP treatment group compared with the placebo treatment group. This was driven by a higher incidence of upper respiratory tract infections, which is considered an ADR for ZLP.

There was a slightly higher incidence of urinary tract infections in the ZLP group compared with the placebo group (8 study participants [6.3%] vs 4 study participants (3.4%), respectively) in the HLT Urinary tract infections and 1 study participant (0.8%) with PTs urinary tract infection pseudomonal and Escherichia urinary tract infection in the placebo and ZLP groups, respectively.

Serious infections

Table 37: Incidence of serious infection TEAEs (Pool S2A)

MedDRA v24.0 SOC HLT PT	Placebo N=118 n (%) [#]	ZLP 0.1mg/kg+0.3mg/kg N=127 n (%) [#]
Infections and infestations	6 (5.1) [8]	6 (4.7) [9]
Abdominal and gastrointestinal infections	0	1 (0.8) [2]
Abdominal abscess	0	1 (0.8) [1]
Diverticulitis	0	1 (0.8) [1]
Bacterial infections NEC	0	1 (0.8) [1]
Cellulitis	0	1 (0.8) [1]
Candida infections	0	1 (0.8) [2]
Oesophageal candidiasis	0	1 (0.8) [1]
Oral candidiasis	0	1 (0.8) [1]
Coronavirus infections	3 (2.5) [4]	1 (0.8) [2]
COVID-19	2 (1.7) [2]	1 (0.8) [1]
COVID-19 pneumonia	2 (1.7) [2]	1 (0.8) [1]
Herpes viral infections	1 (0.8) [1]	0
Herpes simplex meningoencephalitis	1 (0.8) [1]	0
Lower respiratory tract and lung infections	0	1 (0.8) [1]
Pneumonia	0	1 (0.8) [1]
Rhinoviral infections	1 (0.8) [1]	0
Rhinovirus infection	1 (0.8) [1]	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	1 (0.8) [1]
Sepsis	0	1 (0.8) [1]
Urinary tract infections	1 (0.8) [2]	0
Urinary tract infection	1 (0.8) [2]	0

COVID-19=coronadisease 2019; HLT=High Level Term; ISS=Invirus tegrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of participants reporting a TEAE within HLT/PT.
Note: [#] is the number of individual occurrences of the TEAE.

In the placebo-controlled Pools S1A and S2A, the overall incidence of serious infections was similar in placebo and ZLP treatment groups.

Exposure-adjusted incidence rates and event rates for serious and nonserious infections decreased in the long-term Pools S1B and S2B as compared with the corresponding placebo-controlled Pools S1A and S2A.

***Neisseria* infections**

Background: Zilucoplan is a selective immunosuppressant with a mechanism of action 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). This is supported by experience with approved drugs with a similar mechanism of action eculizumab (Soliris®) and ravulizumab (Ultomiris®), and evidence from patients with genetic deficiencies of terminal complement components. Zilucoplan does not inhibit early complement components, for which deficiencies are associated with an increased susceptibility for a number of other infections, e.g., with other encapsulated bacteria (Lewis and Ram, 2020; Skattum et al, 2011).

No Neisseria infections were reported in the ZLP development programme as of the clinical cutoff date, where all study participants (N=591 including estimated exposure from non UCB sponsored studies) were required to be vaccinated against meningococcal infections and/or to use prophylactic antibiotics.

Opportunistic infections

Potential opportunistic infections were identified through a medical review by checking event PTs or pathogens mentioned in the SAE narrative with the MedDRA Standardized MedDRA Query (SMQ) 'Opportunistic infections.'

In terms of potential opportunistic infections, 3 events of serious infections met the criteria for the narrow scope SMQ:

- Herpes simplex meningoencephalitis: the event started when the subject was on placebo in MG0010 and was reported as worsening on the first day of MG0011 (7 hours after the first ZLP administration), which is not suggestive for a causal involvement of ZLP.

- Endocarditis: different pathogens were identified including *Candida albicans* and *Stenotrophomonas maltophilia*. The event was attributed to a device (cardiac pacemaker) and the study participant had a Hickman catheter for total parenteral nutrition.

- Liver abscess: the event occurred in the context of a post-Endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in a participant with a history of cholecystitis; different pathogens were identified including *Candida albicans*.

Further medical review, also considering terms in the broad scope SMQ, that is known to include less specific terms, identified an additional 10 serious events in 7 study participants:

- Sepsis: following PLEX treatment for a myasthenic crisis; *Staphylococcus aureus* (methicillin-sensitive) was identified.

- Staphylococcal infection: Methicillin-resistant *Staphylococcus aureus* infection post shoulder surgery. The participant also had a central catheter.

- Pneumonia: with coagulase-negative staphylococci and suspected bacteremia with *Staphylococcus hominis*, likely due to contamination. The study participant likely had an intravenous line to administer the vancomycin treatment for pneumonia.

- Bacteraemia with *Acinetobacter, Corynebacterium, and Staphylococcus epidermidis*, attributed most likely to an infected Hickman catheter for total parenteral nutrition.

- Pneumonia klebsiella: urinary tract infection/epididymitis with *Klebsiella pneumoniae*.

- Sepsis (3 separate events) and hepatitis C: 1 sepsis event associated to a pneumonia with *Enterobacter cloacae* in blood cultures, 1 sepsis event related to COVID-19, and a post-procedural

sepsis event in the frame of a post-ERCP pancreatitis. Hepatitis C was reported as a chronic asymptomatic infection related to a needlestick injury, and the participant had a history of ongoing glucose tolerance impairment.

- Staphylococcal sepsis: *Staphylococcus aureus* sepsis with central catheter as probable origin.

In all of these cases, risk factors for opportunistic infections were present, e.g., use of dentures and history of candidiasis in the case of esophageal candidiasis, and also included concurrent use of prednisone or methotrexate.

Potential opportunistic infections occurred at a similar incidence in placebo and ZLP treatment groups in placebo-controlled pools and were overall confounded by concurrent use of immunosuppressants, medical history, presence of intravenous lines/catheters, invasive medical devices/procedures or other factors that are nonsuggestive for causal involvement of ZLP.

Malignancies

In Pool S1A, any TEAEs related to malignant or unspecified tumours were reported by 3 study participants (3.0%) in the ZLP 0.1mg/kg+0.3mg/kg group and 0 study participants in the placebo treatment group. Two events of basal cell carcinoma; 1 mild and 1 moderate in intensity and 2 events of squamous cell carcinoma, both mild in intensity, were reported in the ZLP 0.1mg/kg+0.3mg/kg group. There were no malignancies reported in the IMNM study IMNM01.

In Pool S1B and Pool S2B, TEAEs of interest of malignant tumours were reported by 8 study participants (3.8%) and 8 study participants (3.4%) in All ZLP group, respectively. Preferred terms in this category were basal cell carcinoma, squamous cell carcinoma, malignant melanoma, metastatic malignant melanoma, metastatic neoplasm, and pancreatic carcinoma. The most frequently reported TEAE of malignant or unspecified tumours in Pool S1B and Pool S2B was basal cell carcinoma (4 study participants [1.9%] and [1.7%] each).

Injection site reactions

Table 38: Incidence of Injection site reactions (Pool S1A and Pool S2A excluding MG0009 study participants)

MedDRA v24.0 SOC PT	**Pool S1A**		**Pool S2A**	
	Placebo N=88 n (%) [#]	**ZLP 0.3mg/kg N=86 n (%)[#]**	**Placebo N=103 n (%)[#]**	**ZLP 0.3mg/kg N=98 n (%)[#]**
Any Injection Site Reactions	13 (14.8) [15]	23 (26.7) [33]	14 (13.6) [17]	26 (26.5) [36]
General disorders and administration site conditions	13 (14.8) [15]	23 (26.7) [33]	14 (13.6) [17]	26 (26.5) [36]
Injection site bruising	8 (9.1) [10]	14 (16.3) [18]	9 (8.7) [12]	14 (14.3) [18]
Injection site pain	3 (3.4) [3]	8 (9.3) [9]	3 (2.9) [3]	9 (9.2) [10]
Injection site haematoma	0	2 (2.3) [2]	0	2 (2.0) [2]
Injection site rash	2 (2.3) [2]	0	2 (1.9) [2]	0
Injection site haemorrhage	0	1 (1.2) [1]	0	1 (1.0) [1]
Injection site mass	0	1 (1.2) [1]	0	1 (1.0) [1]
Injection site nodule	0	1 (1.2) [1]	0	1 (1.0) [1]
Injection site reaction	0	1 (1.2) [1]	0	1 (1.0) [1]

MedDRA v24.0 SOC PT	Pool S1A		Pool S2A	
	Placebo N=88 n (%) [#]	ZLP 0.3mg/kg N=86 n (%)[#]	Placebo N=103 n (%)[#]	ZLP 0.3mg/kg N=98 n (%)[#]
Injection site erythema	0	0	0	1 (1.0) [1]
Injection site pruritus	0	0	0	1 (1.0) [1]

ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of study participants reporting at least 1 TEAE within PT.
Note: [#] is the number of individual occurrences of the TEAE.
Note: Injection site reactions: TEAEs in MedDRA High Level Term "Injection site reactions" or High Level Term "Administration site reactions

In Pool S1A, the incidence of TEAEs of interest of Injection site reactions was higher in the ZLP 0.3mg/kg treatment group (23 study participants [26.7%]) compared with the placebo treatment group (13 study participants [14.8%]). The incidence of TEAEs of interest of Injection site reactions in Pool S2A was similar to Pool S1A (26 study participants [26.5%] in the ZLP 0.3mg/kg group and 14 study participants [13.6%] in the placebo treatment group). None of the TEAEs of interest in the event category of Injection site reactions were considered serious or severe, and none resulted in permanent withdrawal from IMP. Injection site reactions is considered an ADR for zilucoplan.

Hypersensitivity reactions including anaphylaxis

In Pool S1A and S2A, incidences of Hypersensitivity reactions respectively were slightly higher and similar in the ZLP 0.1mg/kg+0.3mg/kg group (13 study participants [11.3%] and 13 study participants [10.2%]) compared with the placebo treatment group (9 study participants [8.7%] and 10 study participants [8.5%]). No severe TEAEs of Hypersensitivity reactions were reported across the treatment groups.

The EAIRs and event rates for hypersensitivity reactions were lower or similar in the long-term Pools S1B and S2B as compared with the placebo-controlled Pools S1A and S2A. No events of anaphylactic reactions to ZLP were identified across the pools.

Hepatic events

There were no signs of increased hepatic events compared to placebo.

Skin and oral mucosal ulcerations

In the Phase 2 MG0009 study, study participants were monitored at each study visit for AEs due to skin or oral lesions, and study drug was to be permanently discontinued in the event of moderate or severe skin or oral lesions considered related to study drug. No such events occurred in MG0009.

Table 39: Skin and oral mucosal ulcerations (Pool S2A)

MedDRA v24.0 **HLT** **PT**	**Placebo** **N=118** **n (%) [#]**	**ZLP** **0.1mg/kg+0.3mg/kg** **N=127** **n (%) [#]**
Stomatitis and ulceration	2 (1.7) [2]	5 (3.9) [6]
Aphthous ulcer	0	3 (2.4) [4]
Mouth ulceration	1 (0.8) [1]	2 (1.6) [2]
Lip ulceration	1 (0.8) [1]	0

ISS=Integrated Summary of Safety; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; ZLP=zilucoplan
Note: n=number of participants reporting a TEAE within HLT/PT
Note: [#] is the number of individual occurrences of the TEAE

In the placebo-controlled Pools S1A and S2A, the overall incidence of skin and oral mucosal ulcerations was similar across the ZLP and placebo groups. No events of skin and oral mucosal ulcerations occurred in the Phase 2 IMNM01 study, so there are no differences in these events between Pools S2A and S1A. Exposure-adjusted incidence rates and event rates of skin and oral mucosal ulcerations decreased in the long-term Pools S1B and S2B as compared with the corresponding placebo-controlled Pools S1A and S2A.

Morphoea

Morphoea, also known as localised scleroderma, is a rare idiopathic, inflammatory disorder that causes sclerotic changes in the skin, manifesting as painless, discoloured patches on the skin.

During the MA assessment procedure, a safety signal of morphoea was validated in Feb 2023 by the applicant due to the occurrence of 11 TEAEs of morphoea in 10 study participants in the ongoing open-label Phase 3 study in generalised myasthenia gravis (gMG), MG0011. The time to onset was >1 year, ranging from 430 to 1262 days from the first ZLP dose. The incidence rate of morphoea in the ZLP clinical development programme is 1.90 per 100 patient-years (1900 per 100,000 patient years; 2 TEAEs not included since they both occurred after the cut-off date of the Q1 2023 SSD) while the overall incidence rate of morphoea in the general population reported in the literature ranged from 0.34 (localised scleroderma in children) (Herrick et al, 2010) to 2.7 per 100,000 (Peterson et al, 1997). The applicant concludes that the incidence is considerably higher than reported for the general population. The time to onset is compatible with a drug-induced morphoea, as other drugs implicated as a trigger for morphoea have observed longer latencies consistent with >1 year.

The applicant concludes that although other autoimmune diseases (including scleroderma) are more common in patients with myasthenia gravis than in the general population, morphoea has previously only been described in isolated case reports in MG patients. This may partly be due to a possible underreporting of morphoea related to the mild manifestations of the disease.

Confounding factors among the 10 cases were previous tick bites with Lyme disease (N=1), covid infection or covid vaccination (N=4).

Other C5 inhibitors, eculizumab and ravulizumab, are not labelled for morphoea or scleroderma as ADR in their respective EU SmPCs or US PI; however, there have been reports of morphoea or scleroderma in the post-marketing setting.

Based on the high incidence in the long-term FU study and a time-to-onset that is in line with other drug-induced cases of morphoea, the relation to treatment with zilucoplan is considered at least possible.

Thus, morphoea is included in the SmPC section 4.8 Table of ADRs with a frequency of common and described below the ADR table as a selected ADR.

2.6.8.5. Laboratory findings

Liver function tests

Post-Baseline for Pool S1A and Pool S2A, the incidence of elevated liver function tests was low and similar across treatment groups. No study participants met the laboratory criteria for potential drug-induced liver injuries, including Hy's law criteria ([aspartate aminotransferase or alanine aminotransferase >3.0×ULN] and total bilirubin >2.0×ULN and alkaline phosphatase <2.0×ULN).

Amylase and lipase increased

In the placebo-controlled Pools S1A and S2A, the overall incidence for laboratory abnormalities of amylase increased and lipase increased were higher in the ZLP treatment group compared with placebo. The majority of study participants with laboratory amylase and lipase elevations had a normal Baseline value. Pancreatic enzyme elevations were generally transient and resolved over time with continuation of ZLP. Exposure-adjusted incidence rates for amylase and lipase elevations in these study participants decreased in the long-term Pools S1B and S2B as compared with the corresponding placebo-controlled Pools S1A and S2A.

Table 40: Maximum post-baseline CTCAE grade in study participants with pancreatic enzyme abnormalities (Pool S2A)

Post-baseline laboratory abnormality	Placebo N=118 n (%)			ZLP 0.1mg/kg+0.3mg/kg N=127 n (%)		
	All Grades	Grade 1-2	Grade 3-4	All Grades	Grade 1-2	Grade 3-4
Amylase increased	22 (18.6)	22 (18.6)	0 (0)	32 (25.2)	24 (18.9)	8 (6.3)
Lipase increased	16 (13.6)	10 (8.5)	6 (5.1)	42 (33.1)	27 (21.3)	15 (11.8)

CI=confidence interval; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety; ZLP=zilucoplan
Note: n=number of participants reporting a TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the TEAE.
Definitions of CTCAE grades (V.5): Grade 1 is >ULN-1.5xULN, Grade 2 is >1.5-2.0xULN, Grade 3 is >2.0-5.0xULN, Grade 4 is >5.0xULN.

One study participant (MG0011-122-145) discontinued ZLP due to a pancreatic enzyme elevation. This study participant with a history of rheumatoid arthritis and obesity experienced Grade 3 lipase/Grade 2 amylase with TEAEs of amylase increased and lipase increased reported 57 days after the first dose of ZLP along with other TEAEs of diarrhoea, dyspepsia, and nephrolithiasis. Zilucoplan was interrupted and pancreatic enzyme elevations resolved. After restarting ZLP, the study participant experienced a Grade 1 lipase increase with a TEAE of lipase increased reported along with other TEAEs of abdominal pain, diarrhoea, and vomiting. The participant received a COVID-19 vaccine 13 days prior to the second event of lipase increased. Zilucoplan was discontinued, and lipase elevation resolved. No TEAE of pancreatitis was reported. All TEAEs of amylase increased and lipase increased were considered treatment related by the Investigator. Although a positive rechallenge was observed, it is difficult to interpret the relevance due to the large variability of pancreatic enzyme values over time. This case was confounded by the nephrolithiasis, COVID-19 vaccine, and a history of rheumatoid arthritis.

Three events of pancreatitis were reported, two serious, severe cases presented 24 hours after ERCP and 1 nonserious, mild case occurred 7 days after receiving a COVID-19 vaccine. Pancreatitis is a common severe complication of ERCP, and cases of pancreatitis have been reported in the literature after the COVID-19 vaccine (Arata et al, 2010; Parkash, 2021). Zilucoplan was continued in all cases with resolution of pancreatitis in 2 cases and no resolution in 1 case but normal pancreatic enzyme values at the time of Safety Follow-Up visit; no reoccurrence of pancreatitis was reported in these study participants.

No evidence suggestive of ZLP-induced pancreatitis or other pancreas pathologies was identified. Pancreatic enzyme elevations in other study participants were generally asymptomatic (not associated with abdominal pain), and none of these met the diagnostic criteria for acute pancreatitis per the American College of Gastroenterology.

Events indicative of other pancreas pathologies included 3 events of pancreatic cyst, 2 events of pancreas infection, 1 event of pancreatic carcinoma, and 1 event of pancreatic mass. The majority of these events were serious, and all were considered not related (by the Investigator). Zilucoplan was continued in all cases, except for 1 study participant who withdrew ZLP due to a fatal pancreatic carcinoma. All remaining events resolved at the time of report, except for 1 pancreatic cyst and 1 pancreatic mass.

Eosinophils increased

Background

In the literature, a role for eosinophils in autoimmunity has been suggested (Diny et al, 2017). Case reports of simultaneous presentation of hypereosinophilic syndrome and myasthenia gravis have also been described (Avni et al, 2006; Ishida et al, 1996). Complement 5a is implicated in inducing eosinophil activation and extravasation (Zeck-Kapp and Kapp, 1995; Zeck Kapp et al, 1995); however the effect of C5 inhibition on eosinophils is unclear.

Laboratory assessments for eosinophils were required at Screening, Baseline, and at regularly scheduled intervals in clinical studies as a routine haematology laboratory assessment. In MG0010, a higher incidence of blood eosinophil elevations was observed in the ZLP treatment group compared with the placebo treatment group, which prompted further review.

Hypereosinophilia is defined as eosinophils $\geq 1.5 \times 109$/L, and hypereosinophilic syndrome is defined as eosinophils $\geq 1.5 \times 109$/L on 2 occasions ≥ 1 month apart, plus organ dysfunction attributable to eosinophilia (Weller and Klion, 2022).

Results:

Table 41: Shift from baseline to maximum post-baseline result for eosinophils (Pool S2A)

Shift from baseline to maximum post-Baseline	**Eosinophils**	
	Placebo N=118 n (%)	**ZLP 0.1mg/kg+0.3mg/kg N=127 n (%)**
Normal to High	1 (0.8)	21 (16.5)
High to High	1 (0.8)	0 (0)
Any to High	**2 (1.7)**	**21 (16.5)**

ISS=Integrated Summary of Safety; ZLP=zilucoplan

The high post-baseline eosinophils in 15 study participants were below 1.5×10^9/L (13 study participants in the ZLP group and 2 study participants in the placebo group) and 6 study participants met the criterion of hypereosinophilia (eosinophils $\geq 1.5 \times 10^9$/L), all in the ZLP treatment group.

Eosinophil elevations were generally transient and resolved with continuation of ZLP. The majority of participants were asymptomatic, and no study participants experienced clinically significant organ dysfunction, hypereosinophilic syndrome, or other eosinophilic pathologies. No eosinophils elevations led to permanent discontinuation or drug interruption of IMP.

Vital signs, ECG

There were no clinically meaningful mean changes from Baseline in vital sign parameters or ECG results.

A separate TQT study (UP0093) was designed to study of the effects of a supratherapeutic dose of ZLP on cardiac repolarisation in healthy adult study participants. The results of UP0093 constitute a negative thorough QT (TQT) study for ZLP.

2.6.8.6. Safety in special populations

Gender

The incidences of any TEAEs, treatment-related TEAEs (as determined by the Investigator), and serious TEAEs were higher and had a difference of ≥5 study participants in the ZLP 0.3mg/kg treatment group in female study participants (45 study participants [86.5%], 21 study participants [40.4%], and 9 study participants [17.3%], respectively) compared with male study participants (21 study participants [61.8%], 7 study participants [20.6%], and 2 study participants [5.9%], respectively).

Age

In the pooled data, 158 of subjects with gMG were in the age group 18-<65 years, 50 were 65 to <75 and 5 were 75 to <85 years of age.

Table 42: Summary of TEAEs overall and by age subgroups (S1A)

Category	Overall		<65 years		≥65 years	
	Placebo N=88 n (%) [#]	ZLP 0.3mg/kg N=86 n (%) [#]	Placebo N=62 n (%) [#]	ZLP 0.3mg/kg N=64 n (%) [#]	Placebo N=26 n (%) [#]	ZLP 0.3mg/kg N=22 n (%) [#]
Any TEAEs	62 (70.5) [222]	66 (76.7) [291]	47 (75.8) [175]	53 (82.8) [236]	15 (57.7) [47]	13 (59.1) [55]
Serious TEAEs	13 (14.8) [18]	11 (12.8) [15]	12 (19.4) [17]	7 (10.9) [9]	1 (3.8) [1]	4 (18.2) [6]
TEAEs resulting in permanent withdrawal from IMP [a]	2 (2.3) [2]	4 (4.7) [4]	2 (3.2) [2]	3 (4.7) [3]	0	1 (4.5) [1]
Treatment-related TEAEs	22 (25.0) [34]	28 (32.6) [55]	19 (30.6) [31]	25 (39.1) [51]	3 (11.5) [3]	3 (13.6) [4]
Severe TEAEs	11 (12.5) [14]	10 (11.6) [24]	11 (17.7) [14]	5 (7.8) [15]	0	5 (22.7) [9]
All deaths (number of study participants with AEs leading to death) [b]	1	1	1	1	0	0
Deaths (TEAEs leading to death)	1 (1.1) [1]	1 (1.2) [2]	1 (1.6) [1]	1 (1.6) [2]	0	0

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; SS=Safety Set; TEAE=treatment-emergent adverse event; ZLP=zilucoplan
Note: n=number of study participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Treatment-related TEAEs were considered to be related to IMP by the Investigator.
Note: Severe TEAEs were those with CTCAE Grade 3 or above or those without a CTCAE grading classified as 'severe' by the Investigator.
[a] Includes all deaths.
[b] All deaths were based on all study participants screened and refers to all deaths that occurred on study.

In the age subgroup of ≥65 years, trends between the treatment groups in the incidences of TEAEs, including TEAEs resulting in permanent withdrawal from IMP was similar to that observed in the overall population; trends in the incidences of any TEAEs, severe TEAEs, treatment-related TEAEs (as determined by the Investigator), and serious TEAEs were different to that observed in the overall population (Table 42).

By body weight or BMI

There were no clinically meaningful differences within the subgroups of body weight or BMI.

By disease duration, by MGFA disease class, by gMG refractory status

In the pivotal study MG0010, in the subgroup with ≥median disease duration at baseline, the incidences of TEAEs were higher compared with the subgroup with <median disease duration. The same was true for patients with MGFA disease class III vs II and for those with a gMG refractory status.

Extrinsic factors (Geographic region)

The study regions were East Asia, Europe, and North America.

In general, there were no clinically meaningful differences within the subgroup of geographic region.

Use in pregnancy and lactation

Pregnancy

Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development.

Data collected from an ex-vivo closed-circuit human placental transfer model suggest low transfer rate of ZLP (0.5 to 1.0%) in the foetal compartment. The transfer rate of 0.5% was observed at a steady state plasma concentration of 10µg/mL ZLP, corresponding to a therapeutic dose of 0.3mg/kg. The clinical relevance of these data in human pregnancies is unknown.

1 pregnancy case was reported with maternal exposure to ZLP. One study participant from MG0009, who was in the placebo group during the Main Portion of the study and in the ZLP 0.1mg/kg/day dose group in the Extension Portion of the study, became pregnant after discontinuation of ZLP 0.1mg/kg in the Extension Portion, with the date of last menstrual period 1 day before the last ZLP administration. The participant had been exposed to ZLP for more than a year. During pregnancy, the mother experienced gestational diabetes and went on to have an uncomplicated full-term, live birth of a healthy baby via an elective cesarean section. No congenital malformations, failure to thrive, or developmental delay were observed in a follow-up about 16 months after delivery.

Lactation

No cases of lactation were reported with maternal exposure to ZLP. It is unknown whether ZLP is excreted in human milk or absorbed systemically after oral ingestion by the baby.

2.6.8.7. Immunological events

AEs by ADA status and by anti-PEG antibody status

In pool S1B, 2 out of 169 study participants (1.2%) were treatment-emergent ADA positive. Both these subjects had TEAEs of injection site reactions: injection site pain (2 study participants) and injection site bruising (1 study participant).

In pool S1B, 10 out of 169 study participants (5.9%) were treatment-emergent APA positive. TEAEs of injection site reactions were reported in 3 of these subjects and were TEAEs of injection site lump, injection site haemorrhage, and injection site pain (1 study participant each). TEAEs of hypersensitivity reactions were reported in 3 study participants and were TEAEs of dermatitis contact, rash, rash pruritic, and urticaria (1 study participant each).

Overall, incidences of treatment-emergent ADA positive or APA positive study participants were low. Upon review of the available data, no evidence was identified of an association between positive ADA status or positive APA status and the incidence of TEAEs overall, or specifically with hypersensitivity reactions, injection site reactions or autoimmune disorders. Immunogenicity had no clinically meaningful impact on safety of ZLP.

2.6.8.8. Discontinuation due to adverse events

In Pool S1A, the number of participants reporting TEAEs leading to discontinuation was low overall and similar across treatment groups (ZLP 0.3mg/kg [4.0%] and placebo [1.9%]). No TEAEs leading to IMP discontinuation were reported in the ZLP 0.1mg/kg group. Treatment-emergent AEs leading to discontinuation were spread across SOCs with no obvious trend. By PT, no TEAE leading to study discontinuation was reported by >1 study participant in any treatment group.

2.6.9. Discussion on clinical safety

The evaluation of safety of zilucoplan in the treatment of patients with gMG is based on data from the 3 studies included in the present application, the phase 2 study including both the 0.1 and 0.3 mg/kg dose, the phase 3 study with only the 0.3 mg/kg dose vs placebo and the ongoing open-label extension study with patients having completed the main studies. In addition, to enlarge the somewhat small safety database for zilucoplan, patients with a similar disease, IMNM have been included for some safety analyses.

For gMG, 91 subjects have been exposed for more than a year to the therapeutic dose of 0.3 mg/kg. Therefore, the applicant has created safety pool S2B to include subjects with IMNM, a disease with similar clinical characteristics. In safety pool S2B, 99 subjects have been exposed to zilucoplan for at least 12 months. Thus, when including patients with the similar disease IMNM, almost 100 patients have been exposed to zilucoplan for at least 12 months, which is in line with the recommendations for the size of the safety database.

Updated safety data from the ongoing MG0011 clinical trial through the September 8, 2022 cut-off date, provided by the applicant during the procedure did not raise any new safety issue. 139 patients were treated with ZLP for 1 year. This seems sufficient for long term data.

The applicant states that they consider gMG and IMNM studies similar in their randomised controlled trial design and the diseases also similar enough to justify pooling of safety. This may be concurred. However, the safety pools with only gMG patients are preferred in this safety report.

There was no increase in overall incidence of TEAEs or severe TEAEs for zilucoplan-treated patients compared to the placebo group.

The safety data in SmPC section 4.8 stems from Pool S1A with only patients with gMG. Urinary tract infection (UTI) is not included in 4.8 although 7.0% vs 3.9%, since a higher proportion of the zilucoplan study participants had risk factors for UTI compared to the placebo group.

The identified ADRs of zilucoplan for treatment of gMG are injection site reactions, upper respiratory tract infections, diarrhoea, and increased amylase, lipase and blood eosinophils. For the C5 monoclonal antibodies Soliris (eculizumab) and Ultomiris (ravulizumab), upper respiratory tract infections and diarrhoea are also included in the list of ADRs. Thus, these ADRs seem to be class effects. In addition, both these have headache as a very common ADR. However, headache has not been listed as an ADR for zilucoplan, since it was not more frequent in the treatment group than in the placebo group (19.1% vs 16.5% for placebo).

Since the dose range in the gMG and IMNM studies was narrow (0.1 and 0.3 mg/kg) and the number of patients treated with the 0.1 mg/kg dose was low (N=15), no dose-related safety has been identified.

The incidence of any TEAE decreased after the first month of treatment in both zilucoplan treatment groups and placebo groups. In the open-label long-term treatment safety pools, the incidence of any TEAE over time was generally stable, i.e. no meaningful differences in incidence of TEAEs by duration of treatment.

No apparent withdrawal effects after cessation of treatment have been observed in any ZLP study.

In the randomised controlled trials studies, there were 2 deaths, one in the zilucoplan treatment group (Covid-19 pneumonia, after 18 days exposure to zilucoplan) and one in the placebo group (cerebral haemorrhage). Nine deaths occurred during OLE periods (3 in MG0009, 5 in MG0011, and 1 in IMNM01) after a mean (median) exposure period of 10.9 (6.2) months (range 2.5-42.2 months) to zilucoplan. Among these 9 OLE deaths, 2 were related to covid-19 infection, in 3 cases the reported cause of death was cardiac arrest, 1 due to head injury, 2 had pancreatic carcinoma or probable pancreas cancer at the

time of death, 1 was due to pneumonia. None of the deaths were considered treatment-related by the Investigator. There were several death cases in which the patient was described as having confounding factors related to metabolic syndrome; diabetes in 8 cases, hypertension in 7, hypercholesterolemia or hyperlipidaemia in 5, and obesity in 3.

Pancreatic events are interesting, since there were pancreatic events in the cynomolgus non-clinical studies and elevated amylase and lipase and 3 cases of pancreatitis in the clinical studies. However, the patients with pancreatic cancer had been on zilucoplan treatment at the 0.3 mg/kg dose for 230 and 241 days at the time of death, respectively. The pancreas cancer and pancreatic mass were diagnosed 6 months and 3 months after initiation of zilucoplan treatment, respectively, making zilucoplan treatment an unlikely cause or contributing factor for the malignancy.

The incidence of SAEs was equal between treated and placebo groups. However, within the various SOCs there were slightly more serious infections in the zilucoplan group, counterbalanced by more SAEs with the term myasthenia gravis in the placebo group, the latter being indicative of a positive treatment effect.

The number of TEAEs leading to discontinuation was overall low and similar across treatment groups.

Based on the experience from the C5 monoclonal antibodies eculizumab and ravulizumab and non-clinical studies of zilucoplan, the applicant had defined several AEs of interest, which included infections, Neisseria infections, opportunistic infections, malignancies, injection site reactions, hypersensitivity reactions, hepatic events skin and oral mucosal ulcerations, and pancreatic events.

The overall incidence of non-serious infections was higher for zilucoplan-treated subjects than for placebo (26.0% vs 14.4%), which was driven by a higher incidence of upper respiratory tract infections (12.6% for ZLP vs 5.9% for placebo), which is considered an ADR for ZLP. The incidence of UTI was slightly higher in the ZLP group compared with the placebo group (6.3% vs 3.4%).

In the placebo-controlled Pools S1A and S2A, the overall incidence of serious infections was similar in placebo and ZLP treatment groups. Serious infections have been included as an important potential risk in the list of safety concerns in the context of the PSUR.

Meningococcal infections are the most important identified risk for C5 inhibition, since it is cleared via the MAC, the formation of which is inhibited by zilucoplan treatment. In the present studies, all study participants were required to be vaccinated against Neisseria Meningitidis (meningococcal infection) and/or to use prophylactic antibiotics. As a result, no meningococcal infections were reported in the ZLP development programme. Post-marketing, all patients are required to be vaccinated against Neisseria Meningitidis at least 2 weeks before zilucoplan treatment, or otherwise use antibiotics until at least 2 weeks have passed after the vaccination. Since patients with generalised myasthenia gravis are at higher risk of contracting infections due to their muscle weaknesses including the respiratory muscles, it would be prudent to be consistent with the immunisation recommendations in the SmPC even though no actual increase in the risk for serious infections (other than Neisseria) has been identified for zilucoplan. However, elderly as well as patients with diseases leading to muscle weakness (such as gMG) are often recommended to be vaccinated against pneumococcal infections. As a general precautionary principle and in line with the C5 antibodies and treatment guidelines, the following is added to the SmPC 4.4 text: "Prior to initiating zilucoplan therapy, it is recommended that patients initiate immunizations according to current immunization guidelines."

With regards to the risk of malignancy after zilucoplan treatment, no increased risk has been seen in non-clinical studies and in subjects with a genetic C5 deficiency. Malignant tumours were reported in 8 patients in the OLE studies, but these numbers were not considered increased compared to the normal population and did not include any cancer types that are known to be secondary to viral infection, such as HPV-related cervical cancer.

The incidence of injection site reactions was higher in the zilucoplan 0.3 mg/kg treatment group than in the placebo group (26.7% vs 14.8%) in pool S1A with similar numbers when the IMNM study was included in pool S2A. Injection site reactions are considered ADRs of zilucoplan. The incidence of hypersensitivity reactions was slightly higher in the zilucoplan treated groups than in the placebo groups over the randomised controlled trial pools. No severe hypersensitivity reactions including anaphylactic reactions occurred. Unlike the non-clinical cynomolgus toxicology studies, there were neither signs of hepatic events nor an increased incidence of skin and oral mucosal ulcerations in the clinical studies of zilucoplan.

Transient amylase and lipase elevations were seen without corresponding cases of pancreatitis.

Other C5 inhibitors, eculizumab and ravulizumab, are not labelled for any pancreatic events in their respective EU SmPCs; however, there have been reports of pancreatic events, including pancreatitis, pancreatic cysts, pancreatic carcinoma, pancreatic enzymes increased in the post-marketing setting, (FAERS dashboard, 2023).

The incidence of elevated liver function tests was low and similar across treatment groups. No study participants met criteria for potential drug induced liver injuries, including Hy's law criteria and no hepatic events occurred in the clinical studies.

In total, 12 pancreatic events in 9 subjects (8 men and 1 female), occurred. Infections were reported in the same patient prior to or during the pancreatic event in 10 of 12 cases, but no association between infectious agent and the pancreatic event was identified. 4 events of pancreatitis, of which 3 occurred in gMG patients and 1 occurred in an ALS study. Of these, 2 occurred after ERCP and 1 after covid vaccination. ERCP is a well-known risk for pancreatitis. Furthermore, of the pancreatic events, 5 were pancreatic cysts, of which 2 were pseudocysts, which may be a complication of ERCP, 1 was a benign epithelial cyst, 1 was a multifocal branch-duct intraductal papillary mucinous neoplasm (BD-IPMN, which shows a lower risk than main duct IPMN to develop into pancreatic cancer) and 1 unknown type. Known risk factors for acute pancreatitis are gallstones and the ERCP procedure to treat gallstones, alcohol abuse, smoking, diabetes, obesity. Taking into consideration the non-clinical findings of both hepatobiliary and pancreatic changes, a common causative factor for hepatobiliary and pancreatic events would have been expected in the clinical studies. However, here was no trend for liver enzyme elevations of concern in the clinical studies, which otherwise could have suggested a common causative factor for the original hepatobiliary events treated with ERCP and the pancreatitis.

In conclusion, no common causative factor has been elucidated for severe pancreatic events including acute pancreatitis and pancreatic cancer. Nevertheless, the pancreatic findings in the non-clinical studies together with the elevated pancreatic enzymes in the human studies call for a close follow up of pancreatic events post-approval. Pancreatic events are included as an important potential risk in the list of safety concerns in the context of the PSUR.

A role for eosinophils in autoimmunity has been suggested and complement 5a is implicated in inducing eosinophil activation and extravasation. Case reports of simultaneous presentation of hypereosinophilic syndrome and myasthenia gravis have been described. In the zilucoplan studies, transient asymptomatic eosinophil elevations were observed without cases of hypereosinophilic syndrome.

There were no effects on vital signs or ECG. A negative TQT study was included during the submission.

Not surprisingly, a longer disease duration, a more severe disease, and a refractory disease were all related to a higher incidence of TEAEs in the pivotal study. This probably reflects both a more fragile status of the patient due to muscular weakness and patients with a longer disease duration previously having been exposed to more immunosuppressive medications making them more susceptible to infections. There was also a trend for women having more TEAEs.

The incidence of serious TEAEs in placebo vs zilucoplan-treated patients was variable in different BMI spans, with the higher incidence in zilucoplan vs placebo only in the BMI 30-40 kg/m^2 group. In the OLE study, the two groups with a BMI 30-40 kg/m^2 and >40 kg/m^2 showed an increasing rate of serious TEAEs related to cardiac disorders and infections & infestations.

The applicant claims that an increasing trend for the SOCs Cardiac disorders and Infections and infestations is expected since obese patients have an increased risk of morbidity and mortality for these types of disorders. According to the applicant, obesity and/or comorbid conditions were risk factors for an increased mortality in the types of TEAEs that led to death in all 8 study participants with a BMI >30kg/m2 and that the presence of these risk factors are nonsuggestive for a contributory role of ZLP.

Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy and an ex-vivo closed-circuit human placental transfer model suggest low transfer rate of ZLP (0.5 to 1.0%) in the foetal compartment. The clinical relevance of these data in human pregnancies is unknown.

1 pregnancy with maternal exposure to zilucoplan for a year before and with the last dose shortly after the last menstruation, giving birth to a healthy child. No reported cases of lactation while treated with zilucoplan.

The applicant has presented results from an *ex vivo* placental transfer model indicating low grade transfer of zilucoplan over placenta. However, the clinical relevance of this model is unknown and the data from the literature on placental transfer of peptides and pegylated peptides provided by the applicant did not shed further light on this issue. Thus, there is no clinical information that could justify a specific SmPC text for zilucoplan in section 4.6.

Incidences of treatment-emergent ADA positive or APA positive study participants were low in the long-term safety pool (1.2% and 5.9%, respectively). There was no evidence of an association between positive ADA status or positive APA status and the incidence of hypersensitivity reactions, injection site reactions or autoimmune disorders.

During the procedure, a safety signal of morphoea was validated in Feb 2023 by the applicant due to the occurrence of 11 TEAEs of morphoea in 10 study participants in the ongoing open-label Phase 3 study in gMG, MG0011. Based on the high incidence in the long-term FU study and a time-to-onset that is in line with other drug-induced cases of morphoea, the relation to treatment with zilucoplan is considered at least possible. Thus, morphoea is included in the SmPC section 4.8 Table of ADRs with a frequency of common and described below the ADR table as a selected ADR.

2.6.10. Conclusions on the clinical safety

The safety database is considered sufficient and the safety of zilucoplan in the treatment of gMG has been appropriately characterised. The safety profile is acceptable with *Neisseria* infection being the most important risk. Increases in amylase and lipase appear product specific. It should be further elucidated in PSURs whether pancreatic events including pancreatitis may be a risk for zilucoplan.

Risk Management Plan

2.6.11. Safety concerns

Table 43: Summary of safety concerns

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

2.6.12. Pharmacovigilance plan

Table 44: 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 authorisation in Europe).
			Interim report submission	01 Jun 2026
			Final report submission	01 Dec 2028
MG0011 (RAISE-XT)–- A Phase 3, multicentre, 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=generalised myasthenia gravis; PASS=post-authorisation safety study; PRAC=Pharmacovigilance Risk Assessment Committee; RMM=risk minimisation measure

2.6.13. Risk minimisation measures

Table 45: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk minimisation measures (RMMs)	Pharmacovigilance 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 programme 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 utilised in the post-marketing setting. **Additional PhV activities:** Zilucoplan observational secondary data post-authorisation safety study (MG0026).
Missing information		
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 post-authorisation 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 post-authorisation safety study (MG0026). Zilucoplan open-label extension study (MG0011/RAISE-XT)

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

2.6.14. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date IBD. The IBD is 12-11-2015. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zilbrysq (zilucoplan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this

medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant seeks approval for zilucoplan (Zilbrysq) in the following indication: for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and require treatment in addition to steroids or non-steroidal immunosuppressants.

MG is a rare disease characterised by the production of autoantibodies targeting proteins that are critical for the normal transmission of neurotransmitter signals from nerves to muscles. Approximately 80% of patients with MG are AChR antibody positive. Binding of anti-AChR auto-antibodies to AChR results in an activation of the classical complement pathway, culminating in the cleavage of C5 into C5a and C5b and deposition of the cytolytic MAC (C5b-9) on the post-synaptic membrane of the NMJ and subsequent injury to the neuromuscular endplate.

MG most commonly affects young adult women (under 40) and older men (over 60), but it can occur at any age. The prevalence of MG in Europe (EU) is estimated to be 1 per 5,000 population (Orphanet).

3.1.2. Available therapies and unmet medical need

First-line therapy for symptomatic gMG is treatment with acetylcholinesterase inhibitors such as pyridostigmine. Pyridostigmine monotherapy is usually insufficient for the treatment of generalised weakness. Therefore, corticosteroids with or without systemic immunosuppressants are used off label. Immunosuppressants used frequently in gMG include azathioprine and mycophenolate mofetil. Cyclosporine, methotrexate, tacrolimus, cyclophosphamide, and rituximab are also used. These immunosuppressants have established short- and long-term toxicities. Surgical removal of the thymus may be recommended in patients with non-thymomatous gMG and moderate to severe symptoms, in an effort to reduce the production of AChR autoantibodies. IVIG and PLEX are typically used short-term to manage worsening MG symptoms and in patients with myasthenic crisis or life-threatening signs such as respiratory insufficiency or dysphagia.

Inhibition of C5 for the treatment of gMG has already been shown to be effective in 2 clinical studies with the C5-blocking antibodies eculizumab and ravulizumab. The most recent additions to the MG treatment regimen, has been the introduction of efgartigimod (Vyvgart®), an IgG1 Fc fragment that targets FcRn, leading to reduced overall IgG recycling.

In spite of a number of MG medications used off-label and recently approved, an unmet medical need for new therapies due to insufficiencies of current treatment options due to insufficient effects, adverse effects, high costs, and poor patient access continues to persist. There is a need for improved therapeutic options, and in particular a more accessible and convenient C5 inhibitor such as zilucoplan for patients with gMG.

3.1.3. Main clinical studies

The main clinical trials were the phase III trials MG0010 and its open label extension MG0011.

MG0010 was a single pivotal, placebo-controlled, double- blind parallel study comparing zilucoplan 0.3 mg/kg and placebo. Endpoints were measured at 12 weeks with MG-ADL change from baseline being the primary efficacy endpoint and change from baseline in QMG, MCG and MG-QOL15r as the most important secondary efficacy endpoints. One hundred and seventy-four patients were randomised, 88 to placebo and 86 to zilucoplan.

MG0011 was an open label study for participants who had completed MG0011 or the phase II study MG0009. All participants (N=199) were given zilucoplan 0.3 mg/kg. Efficacy at 24 weeks was obtained by combining the 12 weeks blinded data from MG0010, and 12 weeks open label data from MG0011.

3.2. Favourable effects

Efficacy at 12 weeks: primary and key secondary endpoints

Study MG0010 was a single pivotal, randomised double blind PB-controlled parallel study comparing the efficacy of ZLP 0.3mg/kg with PB at 12 weeks. Patients included were to be Acetylcholine-receptor antibody positive, MGFA II-IV, have at least an MG-ADL score of 6 and a QMG score of at least 12 with a score of at least 2 in at least 4 items. At baseline, MG-ADL was 10.6 and QMG was 19.1, 50.6% of participants were treatment refractory. After 12 weeks of treatment, the primary efficacy endpoint, MG-ADL change from baseline, was LSM -2.09 (95% CI -3.24, -0.95) in ZLP 0.3 mg/kg treated participants, corrected for CBL in PB participants ($p<0.001$). All sensitivity analyses were highly significant with estimates ranging between -2.02 and -2.35. The first key secondary efficacy endpoint, QMG change from baseline, was (LSM) -2.94 (95% CI -4.39, -1.49) corrected for CBL in PB participants ($p<0.001$). Efficacy estimates in the two other key secondary endpoints, MGC and MG-QOL15r, were -3.20 ($p=0.0023$) and -2.49 ($p=0.0128$).

Study MG0009 was a phase II randomised double blind PB-controlled parallel study comparing the efficacy of ZLP 0.3mg/kg and ZLP 0.1mg/kg with PB at 12 weeks. In this study, QMG was the primary efficacy endpoint and MG-ADL one of the secondary endpoints. Baseline characteristics were similar to study MG0010. Efficacy (CBL in QMG) at 12 weeks was -2.8 corrected for CBL in PB treated participants ($p=0.0538$, one-sided p-value). MG-ADL change from baseline was -2.3 corrected for CBL in PB treated participants ($p=0.0392$, one-sided p-value). Efficacy estimates in the two other key secondary endpoints, MGC and MG-QOL15r, were -4.1 ($p=0.0301$, one-sided p-value) and -3.7 ($p=0.0624$, one-sided p-value).

Study MG0011 was an OLE of Study MG0010 (and MG0009) where all participants received ZLP 0.3 mg/kg. After 12 weeks of open label ZLP 0.3 mg/kg treatment, the former MG0010 PB participants had reduced their MG-ADL with 2.87 points and QMG 3. 77 points. This can be compared to the CBL not corrected for PB in study MG0010, MG-ADL -4.68 and QMG -6.48.

Additional efficacy data at 12 weeks

Proportions and odds ratio (ORs) were calculated for responders in Study MG0010: MG-ADL (achieving a ≥3-point reduction in MG-ADL score at Week 12 without rescue therapy), 73.1% (ZLP) vs 46.1% (PB), OR: 3.184; 95% CI: 1.662 to 6.101, QMG (achieving a ≥5-point reduction in QMG score at Week 12 without rescue therapy) 58.0% vs 33.0%, OR: 2.865; 95% CI: 1.518 to 5.409 and Minimal Symptom Expression (MG-ADL of 0 or 1, at Week 12 without rescue therapy) 14.0% vs 5.8%; OR: 2.608; 95% CI: 0.866 to 7.860. MG-ADL responders and QMG responders were significant also after multiplicity control.

The cumulative proportion of study participants receiving rescue therapy by Week 12 was 5% (4 participants) in the ZLP 0.3mg/kg group and 12% (10 participants) in the placebo group (p=0.1003).

Efficacy at 24 weeks: primary and key secondary endpoints

Efficacy at 24 weeks was estimated in participants who received ZLP 0.3 mg/kg blinded for 12 weeks in study MG0010 and continued ZLP 0.3 mg/kg in the OL study MG0011. After 24 weeks of active treatment, the CBL with conservative imputation (participants who discontinued or used rescue therapy were counted as treatment failures and participants who died were given the maximum score for each assessment scale) was -5.33 in MG-ADL and – 7.10 in QMG. CBL in MGC and MG-QOL15r was -9.91 and -8.06, respectively.

24 weeks efficacy data was also obtained from Study MG0009 when combining the 12-week blinded portion with the OL portion of the same study. CBL was -4.15 in MG-ADL, -7.50 in QMG, -7.6 in MGC, and -6.1 in MG-QOL15r.

Long term efficacy

With conservative imputation (study participants who discontinued the study and participants who used rescue therapy were counted as treatment failures, study participants who died were imputed with the worst possible score from the time of death) mean change from double-blind study (MG0010) baseline to week 24 (week 12 of MG0011) and week 60 (week 48 of MG0011) in total scores were: MG-ADL -5.46 and -5.16, QMG -7.10 and -6.44, MGC -10.37 and -8.89, and MG QoL15r -8.09 and -7.22 in the initial PB group. Corresponding changes in the group treated with ZLP from MG0010 baseline were; MG ADL -5.20 and -4.37, QMG -7.19 and -6.15, MGC -11.12 and -9.02, and MG QoL15r -7.96 and -6.09.

Subgroup analyses

In the pivotal study MG0010, participants aged <65 years reduced their MG-ADL with 4.56 points (placebo 2.75), and participants aged ≥65 years reduced their MG-ADL with 5.14 points (placebo 3.08), at 12 weeks. MG-QOL15r was reduced 7.02 points (placebo 3.65) in the younger participants and 3.02 points (placebo 4.54) in the older participants. In MG0011, the corresponding reduction in MG-ADL (not PB corrected) after 12 weeks of ZLP treatment in the former PB participants was 3.57 in participants <65 years and 2.36 in participants ≥65 years; the MG-QOL15r reduction was 6.11 and 2.55 points respectively. In *post hoc* analyses with data imputation (rescue therapy, myasthenic crisis, or death were imputed as treatment failure), LSM change in MG-ADL was -2.22 in participants aged <65 years and –1.99 in participants aged ≥65 years, MG-QOL15r LSM change in was -3.52 in the younger participants and +0.26 in the older participants. At week 24 in MG0011, MG-QOL15r was reduced with 9.39 points in the younger participants and 4.29 in the older participants.

Participants in MG0010 with MG-ADL ≤9 at baseline, reduced MG-ADL with 3.88 points (placebo 2.48) and participants with MG-ADL >9 at baseline reduced MG-ADL with 5.24 points (placebo 3.06) at 12 weeks. Corresponding reductions in MG0011 (not PB corrected) were 1.76 and 6.06 in the former PB participants at 12 weeks and 0.56 and 4.33 in the former ZLP participants (i.e. their last 12 weeks of ZLP treatment). In *post hoc* analysis using imputation (scores after rescue therapy or any death or myasthenic crisis were imputed based on baseline score or on the last available score, whichever was worst) participants with baseline MG-ADL <9, 9-<12, and ≥12, reduced their MG-ADL score with 4.41, 3.49 and 5.59 points respectively (not corrected for BP). Efficacy data based on MG-ADL were not provided for 24 weeks follow up.

Participants with QMG ≤17 at baseline vs ≥18 at MG0010 baseline reduced their MG-ADL with 4.19 points (placebo 2.81) and 5.11 points (placebo 2.88), respectively. Corresponding numbers in MG0011 (i. e. not PB corrected) were -2.43 and -5.05 in the former PB participants at 12 weeks and -0.50 and -3.80 in the former ZLP participants (i.e. their last 12 weeks of ZLP treatment). In *post hoc* analysis using

imputation (scores after rescue therapy or any death or myasthenic crisis were imputed based on baseline score or on the last available score, whichever was worst) participants with baseline QMG ≤16 and QMG >16 (note the different subgroup limits than in the original analyses), reduced their MG-ADL with 3.88 and 4.61 points respectively (not corrected for PB). Efficacy data based on QMG were not provided for 24 week follow up.

Participants classified as MG refractory *yes* versus *no* reduced their MG-ADL with 2.63 and 1.08 respectively, (corrected for PB). Corresponding numbers in MG0011 (i. e. not PB corrected) were -3.87 and -2.67 in the former PB participants at 12 weeks and -0.97 and -1.39 in the former ZLP participants (i.e. their last 2 weeks of ZLP treatment).

3.3. Uncertainties and limitations about favourable effects

The requirements of the disease manifestations, as expressed in the inclusion criteria of studies MG0009 and MG0010, decrease the proportion of patients with mild disease. This can be seen in the baseline disease characteristics where more than 70% of participants had at least moderate weakness according to the MGFA classification, mean MG-ADL was 10.6 and mean QMG (all participants) was 19.1. For comparison, the cohort of patients selected from the MG-registry for the external reference of study MG0011 (requirement of baseline MG-ADL ≥ 6), had a baseline MG-ADL of 7.4 and QMG of 12.9. The two cohorts from the MGTX study included in the modelling for the reference group, had an index mean QMG of 13.0 and mean MG-ADL of 8.0 before using Odds Weighting. Subgroup analyses based on dichotomous groups of disease severity (MG-ADL ≤9 vs >9, QMG ≤17 vs ≥ 18) indicate that participants in the groups with less severe disease improved numerically less than participants more affected by their gMG disease. This is seen in the PB controlled study MG0010 at 12 weeks and the difference between less and more affected participants, albeit not corrected for PB effect, is even larger after 24 weeks in study MG0011. However, *post hoc* subgroup analyses which used data imputation (scores after rescue therapy or any death or myasthenic crisis were imputed based on baseline score or on the last available score, whichever was worst) as opposed to the original subgroup analyses, did not confirm the initial findings. In explored subgroups (based on MG-ADL at baseline, QMG at baseline and MGFA at baseline), no clear correlation was observed between the effect size (CBL, responder rate) of zilucoplan and disease severity. 24 weeks efficacy data in subgroups based on MG-ADL and QMG were not provided.

As pointed out earlier in scientific advice, a 12-week PB-controlled study may not be of sufficient duration, given the expected long-term treatment and the fact that myasthenia gravis fluctuates over time. Twenty-four weeks data were obtained by combining the 12-week double-blind Study MG0010 with the first 12 weeks of the OL study MG0011. The main issue with the last 12 weeks being that in a setting that lacks a concurrent randomised control, treatment efficacy cannot be isolated, and the true treatment efficacy cannot be separated from e.g., subject-expectancy effect or spontaneous disease fluctuations. Nevertheless, supplementary analyses support that there is treatment efficacy after the 12 weeks of open label study (in total 24 weeks) despite other sources of clinical improvement.

In study MG0011, at 12 weeks, there is a numerical difference with smaller efficacy magnitude in participants ≥65 years of age in the former PB participants. The difference is minor in the MG-ADL score, but quite evident in the secondary efficacy endpoints. In Study MG0010, elderly participants seemed to benefit less than younger only when looking at the quality-of-life score, MG-QOL15. In an additional *post hoc* analysis using imputation (discontinuation, rescue and death imputed with treatment failure) a difference in efficacy between age groups in MG0010 was still seen in QMG; -3.42 versus -1.84, and MG-QOL15r -3.52 versus +0.26. A more conservative analysis (death imputed with worst score of each scale) was performed on data from MG0011 and a notable difference between age groups was then only seen for MG-QOL15r in participants treated for 24 weeks.

3.4. Unfavourable effects

The most well-characterised risk of C5-inhibition, known from subjects with genetic C5 deficiency and treatment with the approved C5-blocking monoclonal antibodies eculizumab and ravulizumab is the risk of *Neisseria* infection, and especially that of Neisseria Meningitidis (meningococcal meningitis). Therefore, all subjects in the clinical studies were vaccinated against meningococcal infection and no such cases occurred.

The overall incidence of AEs was similar between study arms (80.9% zilucoplan versus 73.4% placebo) in the phase 2 and 3 studies (Pool S1A), most of them mild-moderate AEs (severe AEs 13.9% zilucoplan versus 13.6% placebo) and 34.8% in zilucoplan versus 26.2% in placebo considered related to treatment. In Pool S1A, incidences of serious TEAEs were similar in the ZLP 0.1mg/kg+0.3mg/kg group (13.9%) and in the placebo group (15.5%). The incidence of AEs leading to treatment discontinuation was also low (4.0% zilucoplan 0.3 mg/kg versus 1.9% placebo, 0 in zilucoplan 0.1 mg/kg group). In the two randomised clinical trials, there were 2 deaths, one in the zilucoplan treatment group (Covid-19 pneumonia) and one in the placebo group (cerebral haemorrhage). Eight deaths occurred during OLE periods of gMG studies (3 in MG0009, 5 in MG0011).

Headache (19.1% versus 16.5% of patients for zilucoplan and placebo, respectively), injection site bruising (13.9% versus 9.7%), myasthenia gravis (12.2% versus 12.6%), diarrhoea (9.6% versus 2.9%), (procedural) contusion (7.8% versus 3.9%), injection site pain (7.0% versus 3.9%), urinary tract infection (7.0% versus 3.9%), amylase increased (6.1% versus 2.9%), lipase increased (5.2% versus 2.9%), nasopharyngitis (5.2% versus 2.9%), oedema peripheral (4.3% versus 1.0%), were the most frequently reported AEs both in zilucoplan and placebo groups. During the open-label extension headache (23.0%), myasthenia gravis (19.7%), and diarrhoea (15.0%). were the most frequently reported AEs. ARDs for zilucoplan (pool S2A) were injection site reactions (25.2% for all zilucoplan treated versus 14.4% for placebo), upper respiratory tract infections (13.4% versus 6.8%), diarrhoea (8.7% versus 2.5%), amylase increased (6.3% versus 2.5%), lipase increased (4.7% versus 2.5%), and blood eosinophils increased (0.8% versus 0).

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties of the unfavourable effects derive from the limitations of the safety database, particularly long-term safety data with a total of 138 gMG patients exposed for ≥6 months and 91 gMG patients exposed for more than a year, of which 87 at the therapeutic dose 0.3mg/kg). When patients with IMNM were included, 99 subjects have been exposed to zilucoplan for ≥12 months. These uncertainties are mitigated to some extent by the long-standing post-marketing experience with other C5 related products. In addition, clinical reviews of rare cases with inherited C5 deficiency show that an increased risk of recurrent *Neisseria* infections appears to be the only clinical consequence of C5 deficiency (Schejbel et al., Primary complement C5 deficiencies – Molecular characterisation and clinical review of two families,2013). Updated safety data from the ongoing MG0011 clinical trial through the September 8, 2022 cut-off date, provided by the applicant during the procedure did not raise any new safety issue. 139 patients were treated with ZLP for 1 year. That seems sufficient for long term data.

The total number of study participants in the ZLP 0.1mg/kg treatment group (N=15) was limited compared with the number of study participants in the placebo (N=118) and ZLP 0.3mg/kg (N=112) treatment groups. This has impeded the detection of potential dose response with respect to safety, since the dose range was narrow between the two doses used in clinical studies and the numbers were too small to draw any meaningful conclusions. Overall, no dose response has been observed with respect to safety.

Due to the limited number of patients enrolled in some categories, it is not possible to obtain any reliable conclusions about different safety profile in specific subgroups. Nevertheless, a trend for a higher incidence of severe and serious AEs is noted in the elderly population and for all AEs and serious AEs for female versus male subjects.

Meningococcal infections are the most important identified risk for C5 inhibition, since it is cleared via the MAC, the formation of which is inhibited by zilucoplan treatment. In the present studies, all study participants were required to be vaccinated against *Neisseria Meningitidis* (meningococcal infection) and/or to use prophylactic antibiotics. As a result, no meningococcal infections were reported in the ZLP development programme. However, upper respiratory tract infections were observed at an increased incidence in the zilucoplan group versus placebo and UTIs were slightly more common. Since patients with gMG may also be more susceptible to infections due to their background disease with respiratory muscular weakness, a recommendation that patients initiate immunisations according to current immunisation guidelines before treatment with zilucoplan is included in SmPC 4.4.

Serious infections have been included as an important potential risk in the list of safety concerns in the context of the PSUR.

No common causative factor has been elucidated for severe pancreatic events including acute pancreatitis and pancreatic cancer. Nevertheless, the pancreatic findings in the non-clinical studies together with the elevated pancreatic enzymes in the human studies call for a close follow up of pancreatic events post-approval. Accordingly, pancreatic events have been included as an important potential risk in the list of safety concerns in the context of the PSUR.

3.6. Effects Table

Table 46: Effects table for Zilbrysq (zilucoplan) for the treatment of generalised myasthenia gravis

The database for the interim Clinical Study Report of MG0011 is based on a clinical data cut-off date of 18 Feb 2022.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
			Zilucoplan 0.3 mg/kg groups	Placebo		
MG-ADL	8-item (0-24p) Patient reported outcome	CBL week 12	-4.39	-2.30	p<0.001 for MG-ADL (primary EP) and QMG first key secondary EP. MGC and MG-QOL15r had p<0.05. Sensitivity analyses with similar estimates and statistical significance. Few discontinued the study.	MG0010
QMG	Standardised and validated quantitative strength scoring (0-39p)	CBL week 12	-6.19	-3.25		
MGC	Combination of examination and patient reported symptoms	CBL week 12	-8.62	-5.42		
MG-QOL15r	Patient reported QOL	CBL week 12	-5.65	-3.16		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
MG-ADL	8-item (0-24p) Patient reported outcome	CBL week E12/ week 24	-5.33	-	Open label. No placebo control. Rescue therapy or discontinuation counted as treatment failure and imputed with last observation or baseline score whichever was worst. Death was imputed with worst score possible for each scale.	MG0011 Interim analysis, cut-off date 08 Sep 2022
QMG	Standardised and validated quantitative strength scoring (0-39p)	CBL week E12/ week 24	-7.10	-		
MGC	Combination of examination and patient reported symptoms	CBL week E12/ week 24	-9.91	-		
MG-QOL15r	Patient reported QOL	CBL week E12/ week 24	-8.06	-		
Unfavourable Effects						
		%	Zilucoplan 0.3 and 0.1 mg/kg groups	Placebo	Percentages calculated based on available data from patients on zilucoplan and patients on PBO.	Pool S1A (MG0009 /MG0010 combined safety analysis)
All AEs		%	80.9	73.4		
Treatment-related AEs		%	34.8	26.2		
Severe AEs		%	13.9	13.6		
AEs leading to treatment discontinuation		%	3.5	1.9		
Headache		%	19.1	16.5		
Injection site reactions		%	26.7	14.8		
Upper respiratory tract infections	Nasopharyngitis, sinusitis, upper respiratory infections. Viral and bacterial	%	13.4	6.8	Pool S2A	
Diarrhoea		%	9.6	2.9		
UTI		%	7.0	3.9		
Amylase increased		%	6.1	2.9		
Lipase increased		%	5.2	2.9		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
ADA		%	1.2	N/A		Pool S1B: (Long-term gMG pool)
Anti-PEG-Ab		%	5.9	N/A		

Abbreviations: CBL change from baseline
Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy at 12 weeks

The primary efficacy endpoint in the phase III trials was change from baseline in MG-ADL. MG-ADL score is a based on the patient's subjective reporting of function and impairment during activities of daily living and a reduction of 2 points indicates clinical improvement (Muppidi *et al*). The efficacy found in the pivotal Study MG0010, a reduction of 2.09 points, can thus be regarded as a clinically relevant effect.

The first key secondary endpoint, change from baseline in QMG, is an important efficacy endpoint as it is based on the physician's examination findings at a specific medical visit when the patient has been off acetylcholine esterase inhibitor medication for a certain number of hours, usually at least 10 hours. It is in that sense objective, as opposed to MG-ADL. It has been found that treatment must produce more than 2.6 units of change in QMG to be of clinical significance. QMG score changes of up to 2.6 units are expected to occur due to variability of repeated observations (Bahron *et al*). Further, the minimal clinically important difference (from baseline) in QMG score has been stated to be dependent on baseline QMG. If baseline QMG >16, a reduction of 2.75 points can be regarded as minimal clinically important difference (Katzberg *et al*). According to the MGFA, recent data support the use of a 2- or 3- point of change in QMG as a criterion for minimal clinically significant change and depending on MG severity; in mild (QMG 0-9) to moderate disease (QMG 10-16), a 2-point change is clinically significant and a 3-point change is significant for severe MG (QMG >16) (https://myasthenia.org/Professionals/Resources-for-Professionals Jan 8, 2023). In the pivotal trial, QMG was reduced with 2.94 points and therefore can be regarded a clinically relevant effect.

MGC, one of the other two secondary endpoints, requires a reduction of 3 points to be considered to reflect clinical improvement and meaningful to the patient. The change from baseline in the pivotal study was -3.20 at 12 weeks. What represents a clinically meaning full change in MG-QOL15r has not been defined.

Based on the above discussion what improvements are required to represent a clinically relevant efficacy, the magnitude of efficacy at 12 weeks in the studied population can be regarded as meaningful. These results were highly significant and robust as sensitivity analyses show similar results with statistical significance.

Efficacy at 24 weeks

It was advised to conduct a 24week placebo controlled phase III trial as MG fluctuates over time and treatment is anticipated to be long lasting. Study MG0011, was an open label extension of the 12-week pivotal study and 60 weeks of active treatment was obtained by adding these together. The main issue with the last 48 weeks is that in a setting that lacks a concurrent randomised control, treatment efficacy

cannot be isolated, and the true treatment efficacy cannot be separated from e.g., subject-expectancy effect or spontaneous disease fluctuations. Nevertheless, supplementary analyses support that there is treatment efficacy after the 12 weeks of open label study (in total 60 weeks) despite other sources of clinical improvement.

Efficacy in patients with mild gMG and patients with MGFA V

Patients included in the ZLP studies were more affected by their disease than in most other published gMG studies. This is likely due to the requirement QMG ≥12 and at least four QMG items of at least score 2, which was not required e. g. in the studies of other authorised gMG products. In subgroup analyses of study MG0010, there was a pattern of smaller magnitude of efficacy in participants with a milder disease. This pattern was also seen in the OL Study MG0011, with the largest difference between patients with mild and moderate-severe disease in participants assessed after the longer treatment duration of 24 weeks. This raised a concern regarding efficacy in patients with mild gMG. Disease severity in gMG can be assessed in several ways and there is no consensus on what should be considered mild disease. In *post hoc* subgroup analyses on data from studies MG0010 and MG0011 using data imputation, no clear correlation was observed between the effect size (CBL, responder rate) of zilucoplan and disease severity (based on MGFA, MG-ADL and QMG). The indication may not be restricted to the pivotal study population, who had QMG ≥12 and at least four QMG items of at least score 2, as it is considered that efficacy can be extrapolated to patients with less severe disease but who are still symptomatic despite standard of care, based on the mechanism of action with reduced complement dependent cytotoxicity.

Patients with severe and life-threatening disease, MGFA V, were excluded from the studies. In line with other authorised gMG products, it is highlighted in the product information that there is no experience in patients of MGFA class V.

Efficacy depending on age and age at disease onset

Subgroup analyses in MG0010 and MG0011 raised some concern regarding efficacy among elderly participants. In *post hoc* analyses using data imputation (discontinuation, rescue treatment or death imputed as treatment failure) there is a numerical difference at 24 weeks of treatment in MG-QOL15r, other endpoints not showing anything notable. As there is no rationale why efficacy would differ depending on age as such, efficacy analyses based on age at disease onset was performed. MG has traditionally been divided in early onset (dominated by women, typically generalised with clear fluctuations) and late onset (increase proportion of men, more ocular symptoms and less pronounced fluctuations). Lately, division into three subgroups based on age at onset has shown purposeful, early <50, late ≥50 to <65 years, very late ≥65 years (Cortés-Vicente *et al*, 2020). *Post hoc* efficacy analyses with conservative imputation show a variability in placebo response which may be due to a variability in the regression to the mean in a study of patients with a fluctuating disease and strict inclusion criteria (Benatar *et al* 2012). Efficacy assessed after ZLP treatment is more stable and seemingly at a relevant size. Efficacy resulting from inhibition of CDC in AChR antibody mediated disease, should likely not be affected by age or age at onset. Most data point to a fair effect in elderly patients and in patients with late and very late onset of disease and a restriction to the indication is not justified.

Efficacy in treatment refractory patients

The estimated efficacy in participants who at baseline were classified as treatment refractory, was numerically larger than in participants not classified as refractory. This may partly be due to refractory participants having a more severe disease, but the result is important as this group of patients is in particular need for a treatment alternative.

Other comments regarding efficacy

Compared to the two other C5 inhibitors recently approved in the EU which are administered IV (every 1 to 2 months), Zilucoplan is administered SC every day. The SC route may be more convenient to patients despite the need for daily injections, and may reduce the burden on healthcare.

Safety

The C5 inhibition caused by zilucoplan especially increases the risk of *Neisseria* infection. However, to increase the awareness among the treating neurologists, the SmPC 4.4 wording is recommended to be updated related to recommendation to adhere to immunisation programmes for patients with neuromuscular disorders with muscular weakness or patients above the age of 65.

Although the mechanism of action of zilucoplan is well-known from approved C5 monoclonal antibodies, zilucoplan is a different type of molecule and may have a somewhat different safety profile, as indicated by various non-clinical findings (e.g. epithelial degeneration and mononuclear cell infiltrates in various tissues and cases of pancreatitis). From the clinical studies, the non-clinical findings are in general not reflected, but there are remaining uncertainties related to observed various severe pancreatic adverse events and their possible causal relation to zilucoplan treatment, which will be followed up by the applicant in future PSURs.

3.7.2. Balance of benefits and risks

The benefit/risk balance is positive.

The favourable effects on a number of different gMG-related endpoints are robust for placebo-controlled treatment up to 12 weeks and long-term efficacy is supported by open label data up to 60 weeks of zilucoplan treatment. Efficacy can be extrapolated to patients not included in the studies with less severe disease but who are still symptomatic despite standard of care. The unfavourable effects are in general mild to moderate and manageable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Zilbrysq is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zilbrysq is not similar to Soliris and Vyvgart within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zilbrysq is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The controlled access programme and educational programme are aimed at further minimizing the important potential risk of meningococcal infection by reinforcing the key safety information available in the Summary of Product Characteristics and the package leaflet.

The MAH shall ensure that in each Member State where zilucoplan is marketed, healthcare professionals (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

The **physician education material** should contain:

- The Summary of Product Characteristics

- Guide for HCPs

The **guide for HCPs** should contain the following key elements:

- A concise introduction to zilucoplan and the purpose of the guide for HCPs.
- The HCP should educate the patient/caregiver on the risk described 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.
    - Emphasise 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 controlled access programme to ensure that only patients who have been vaccinated against Neisseria meningitidis 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.
- Emphasise 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.

The **patient/caregiver information pack** should contain:

- Package leaflet
- Patient alert card
- Patient/carer guide

The **patient alert card** should contain the following key elements:

- A concise introduction to the potential risk of meningococcal infections with zilucoplan as a 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.

The **patient/care guide** should contain the following key elements:

- 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 minimise the risk of meningococcal infections. Emphasise that

meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infection.

- A controlled access programme 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.

The MAH shall send annually a letter to prescribing physicians to remind them to verify and ensure that their patient's vaccination against meningococcal infection is still current according to relevant vaccination guidelines.

The MAH shall implement in each Member State where Zilbrysq is marketed, a controlled access programme 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that zilucoplan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).