

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216834Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA								
Application number(s)	216834								
Priority or standard	Standard								
Submit date(s)	8/31/2022								
Received date(s)	8/31/2022								
PDUFA goal date	11/30/2023								
Division/office	Division of Neurology I (DNI)								
Review completion date	10/16/2023								
Established/proper name	Zilucoplan								
(Proposed) proprietary name	Zilbrysq								
Pharmacologic class	Complement C5 Inhibitor								
Other product name(s)	N/A								
Applicant	UCB, Inc								
Dosage form(s)/formulation(s)	subcutaneous injection								
Dosing regimen	The recommended dosage is administered once daily as a subcutaneous injection based on body weight <table> <tr> <td>Body Weight</td><td>Once Daily Dosage</td></tr> <tr> <td>Less than 56 kg</td><td>16.6 mg</td></tr> <tr> <td>56 kg to less than 77 kg</td><td>23 mg</td></tr> <tr> <td>77 kg and above</td><td>32.4 mg</td></tr> </table>	Body Weight	Once Daily Dosage	Less than 56 kg	16.6 mg	56 kg to less than 77 kg	23 mg	77 kg and above	32.4 mg
Body Weight	Once Daily Dosage								
Less than 56 kg	16.6 mg								
56 kg to less than 77 kg	23 mg								
77 kg and above	32.4 mg								
Applicant-proposed indication(s)/population(s)	For the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive								
SNOMED CT code for proposed indication disease term(s)¹	91637004 Myasthenia Gravis								
Regulatory action	Approval								
Approved dosage (if applicable)	As above								
Approved indication(s)/population(s) (if applicable)	For the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.								
SNOMED CT code for approved indication disease term(s)¹	91637004 Myasthenia Gravis								

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table of Contents

Table of Tables	vii
Table of Figures	xi
Glossary	1
I. Executive Summary	3
1. Summary of Regulatory Action	3
2. Benefit-Risk Assessment.....	4
2.1. Benefit-Risk Framework	4
2.2. Conclusions Regarding Benefit-Risk	8
II. Interdisciplinary Assessment.....	10
3. Introduction	10
3.1. Review Issue List.....	11
3.1.1. Key Efficacy Review Issues.....	11
3.1.2. Key Safety Review Issues	11
3.1.2.1. Pancreatitis and Associated Pancreatic Conditions	11
3.1.2.2. Meningococcal Infection	11
3.1.2.3. Other Serious Infections	12
3.2. Approach to the Clinical Review.....	12
4. Patient Experience Data	14
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology	14
5.1. Nonclinical Assessment of Potential Effectiveness.....	14
5.2. Clinical Pharmacology/Pharmacokinetics	15
6. Efficacy (Evaluation of Benefit)	20
6.1. Assessment of Dose and Potential Effectiveness	20
6.1.1. Assessment of Dose	20
6.1.2. Mechanistic Evidence of Support	22
6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy	24
6.2.1. Results of Pooled Analyses.....	24
6.2.2. Study MG0010	24
6.2.2.1. Design, Study MG0010	24
6.2.2.2. Eligibility Criteria, MG0010	25
6.2.2.3. Statistical Analysis Plan, MG0010.....	25

6.2.2.4. Results of Analyses, Study MG0010.....	27
6.3. Key Efficacy Review Issues	40
7. Safety (Risk and Risk Management).....	40
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	40
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors	41
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience	42
7.3.1. Adverse Events Identified in Postmarket Experiences	42
7.3.2. Expectations on Safety	42
7.3.3. Additional Safety Issues From Other Disciplines.....	42
7.4. FDA Approach to the Safety Review	42
7.5. Adequacy of the Clinical Safety Database	43
7.6. Safety Results	43
7.6.1. Safety Results.....	43
7.6.1.1. Overview of Treatment-Emergent Adverse Events	43
7.6.1.2. Treatment-Emergent (TE) Deaths	45
7.6.1.3. Treatment-Emergent Serious Adverse Events (TESAEs).....	46
7.6.1.4. Adverse Events Leading to Treatment Discontinuation.....	49
7.6.1.5. Treatment-Emergent Adverse Events.....	50
7.6.1.6. Laboratory Findings	52
7.6.1.7. Assessment of Drug-Induced Liver Injury, All Studies	52
7.6.1.8. Vital Signs	53
7.6.1.9. Subgroups	53
7.7. Key Safety Review Issues	54
7.7.1. Pancreatitis and Associated Pancreatic Conditions.....	54
7.7.2. Meningococcal Infection.....	61
7.7.3. Other Serious Infections.....	62
8. Therapeutic Individualization	63
8.1. Intrinsic Factors	63
8.1.1. Renal Impairment.....	63
8.1.2. Hepatic Impairment.....	63
8.1.3. Ethno-Bridging Study	64

8.1.4. Body Weight	64
8.1.5. Other Intrinsic Factors.....	66
8.2. Extrinsic Factors	66
8.2.1. Drug Interactions.....	66
8.3. Plans for Pediatric Drug Development	67
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential	67
9. Product Quality	68
9.1. Device or Combination Product Considerations	68
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review	69
11. Advisory Committee Summary	69
III. Additional Analyses and Information	70
12. Summary of Regulatory History	70
13. Pharmacology Toxicology	71
13.1. Summary Review of Studies Submitted With the Investigational New Drug Application	71
13.2. Individual Reviews of Studies Submitted With the New Drug Application	73
13.2.1. Repeat-Dose Toxicity.....	73
13.2.2. Reproductive and Developmental Toxicity	79
13.2.3. Genetic Toxicology.....	95
14. Clinical Pharmacology	96
14.1. In Vitro Studies.....	96
14.1.1. Plasma Protein Binding.....	96
14.1.2. Blood-to-Plasma Partitioning.....	96
14.1.3. Metabolism of Zilucoplan (Study # 16900, # TR-0160, # TR-0128) ...	97
14.1.4. Inhibition and Induction of CYP Enzymes by Zilucoplan and Metabolite RA102758 (Study # TR-0102, # 18RAPHP3, #20RAPHP3, # 20RAPHP5R3).....	97
14.1.5. Inhibition of Uridine 5'-Diphospho-Glucuronosyltransferase (UGT) Enzymes (Study # TR-0102).....	98
14.1.6. Interaction Potential of Zilucoplan and RA102758 for Drug Transporters (Study # TR-0100, #TR-0101, # TR-0145, Rapharma-12- 23Jan2018, and Rapharma-16-22Aug2019)	99
14.2. In Vivo Studies	100

14.2.1. Study # UP0112 – Single Ascending Dose and Multiple Dose Study	100
14.2.2. Study # UP0113 – Ethno-Bridging Study in Japanese and Caucasian Subjects	104
14.2.3. Study # UP0114 – Renal Impairment Study	106
14.2.4. Study # UP0094 – Hepatic Impairment Study	108
14.2.5. Study # UP0115 – Relative Bioavailability Study (Impact of Injection Sites)	110
14.3. Bioanalytical Method Validation and Performance	112
14.3.1. Pharmacokinetic Bioanalytical Methods.....	112
14.3.2. Pharmacodynamic Bioanalytical Methods.....	113
14.3.2.1. Total C5 Bioanalytical Method	114
14.3.2.2. sRBC Lysis Bioanalytical Method	114
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety...	115
14.4.1. Incidence Rate of ADAs and APAs	116
14.4.2. Impact of ADAs and APAs on Zilucoplan PK	118
14.4.3. Impact of ADAs and APAs on Zilucoplan PD	119
14.4.4. Impact of ADAs and APAs on Zilucoplan Efficacy	120
14.4.5. Impact of ADAs and APAs on Zilucoplan Safety	121
14.5. Pharmacometrics Assessment.....	122
14.5.1. Applicant’s Analysis	122
14.5.2. Reviewer’s Analysis	130
14.6. Pharmacogenetics	135
15. Study/Trial Design	135
15.1. Study MG0009.....	135
15.1.1. Design, Study MG0009.....	136
15.1.2. Eligibility Criteria, Study MG0009.....	136
15.1.3. Statistical Analysis Plan, Study MG0009	136
15.1.4. Demographics, Study MG0009.....	136
16. Efficacy	137
17. Clinical Safety	137
17.1. QT Prolongation	137
17.2. Laboratory Pancreatic Enzyme Analyses	137
18. Clinical Virology	143

19. Clinical Microbiology	143
20. Mechanism of Action/Drug Resistance.....	143
21. Other Drug Development Considerations	143
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)	143
23. Labeling: Key Changes and Considerations	144
23.1. Approved Labeling Types	149
24. Postmarketing Requirements and Commitments	149
25. Financial Disclosure	150
26. References	150
27. Review Team.....	151
27.1. Reviewer Signatures	152

Table of Tables

Table 1. Application Information	i
Table 2. Benefit-Risk Framework.....	4
Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety for Zilucoplan	13
Table 4. Patient Experience Data Submitted or Considered.....	14
Table 5. Phase 1 Clinical Pharmacology Studies in Healthy Volunteers	15
Table 6. Summary of Clinical Pharmacology and Pharmacokinetics.....	16
Table 7. Total Daily Dose by Body Weight Range in Phase 3 Study (MG0010)	18
Table 8. Proposed Total Daily Dosage by Body Weight Range.....	18
Table 9. Phase 2 (MG0009) and Phase 3 (MG0010) Zilucoplan Doses by Weight Brackets.....	21
Table 10. Subject Dispositions – Study MG0010.....	27
Table 11. Subject Baseline Demographics – mITT – Study MG0010	28
Table 12. Subject Baseline Disease Characteristics – mITT – Study MG0010.	29
Table 13. Primary Endpoint Analyses of MG-ADL – mITT – Study MG0010.....	30
Table 14. Sensitivity Analyses After SN 38 for More Details on “ACh Inhibitor Therapy <10 h” Protocol Deviations	31
Table 15. Subject Counts at Baseline and Week 1 to 12 – mITT – Study MG0010	33
Table 16. Sensitivity Analysis of MG-ADL for Missing Data – Study MG0010	34
Table 17. Secondary Endpoint: Change in QMG Score at Week 12– Study MG0010	35
Table 18. Secondary Endpoint: Change in MGC Score at Week 12– Study MG0010	35
Table 19. Secondary Endpoint: Change in MG-QOL15r Score at Week 12– Study MG0010	35
Table 20. Secondary Endpoint: MG-ADL 3-Points Responders at Week 12– MG0010 ..	36
Table 21. Secondary Endpoint: QMG 5-Points Responders at Week 12– MG0010.....	36
Table 22. Age, Gender, and Race Summaries by Treatment Group – Study MG0010.....	37
Table 23. Findings in Subgroup Populations – Age, Gender, and Race – Study MG0010	37
Table 24. Region and Baseline MG-ADL Score Category Summaries by Treatment Group - Study MG0010	38
Table 25. Findings in Subgroup Populations -Region and Baseline MG-ADL Score Category-Study MG0010.....	38
Table 26. Baseline Demographics and Clinical Characteristics, Safety Population, Study MG0010.....	39

Table 27. Estimated Safety Margins.....	41
Table 28. Overview of Adverse Events, Safety Population, Trial mg0010.....	44
Table 29. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial MG0010	46
Table 30. Treatment-Emergent Adverse Events Occurring at Least 5% of Subjects Treated With Zilucoplan and More Frequently Than Placebo, Phase 3 Study MG0010	50
Table 31. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study MG0010	54
Table 32. Summary of Pancreatic AE/SAEs in the Extension Studies MG0009 and MG0011.	55
Table 33. Relationship Between History of a Pancreatic Condition and Subsequent Pancreatic AE in MG0011	57
Table 34. Subjects of Weight >150kg in MG0009, MG0010, and MG0011	65
Table 35. Study Title: A 39-Week Toxicity Study of RA101495 by Subcutaneous Injection in Cynomolgus Monkeys With an 8-Week Recovery Period.....	73
Table 36. Study Methods	74
Table 37. Experimental Design.....	74
Table 38. TK Parameters in Monkeys	76
Table 39. Microscopic Findings - Early Sacrifice (Bold) and End of Dosing (Amended Report)	77
Table 40. Microscopic Findings - End of Recovery Period (Amended Pathology Report)	78
Table 41. Study Title: RA101495 13-Week Subcutaneous Administration Male Fertility Study in the Cynomolgus Monkey With an 8-Week Recovery Phase	79
Table 42. Study Methods	79
Table 43. Study Design.....	80
Table 44. Testicular Data.....	81
Table 45. Organ Weights – Terminal Sacrifice	82
Table 46. Microscopic Observations - Terminal Sacrifice	83
Table 47. Organ Weights – Recovery Sacrifice.....	84
Table 48. Microscopic Observations - Recovery Sacrifice	84
Table 49. TK parameters for RA101495 in Cynomolgus Monkeys.....	85
Table 50. Study Title: RA101495 Enhanced Subcutaneous Study for Effects on Embryo-Fetal and Pre- and Postnatal Development in Cynomolgus Monkeys With Three Months Lactation/Maturation Phase.....	86

Table 51. Study Methods	86
Table 52. Experimental Design.....	86
Table 53. Maternal Complement Factor – EFD Phase	87
Table 54. Pregnancy Outcome - EFD Phase.....	88
Table 55. Fetal Findings at Cesarean Section.....	89
Table 56. Maternal Complement Factor – ePPND Phase.....	90
Table 57. Pregnancy Outcome – ePPND Phase.....	91
Table 58. Pregnancy Outcome and Infant Loss	91
Table 59. Survival Indices	92
Table 60. Infant Body Weight Change	92
Table 61. TK Parameters for RA101495 in Pregnant Monkeys on GDs 20 and 142.....	94
Table 62. Study Title: Zilucoplan [RA101495]: Micronucleus Test in Bone Marrow Cells of the Sprague-Dawley Rat.....	95
Table 63. Micronucleated PCEs After RA101495 Administration to SD Rats.....	95
Table 64. In Vitro Assessment of Plasma Protein Binding for Zilucoplan, RA102758, and RA103488	96
Table 65. Blood Partitioning of Zilucoplan	96
Table 66. Summary of CYP Isoform Reversible Inhibition by Zilucoplan or RA102758	98
Table 67. Summary of CYP Induction by Zilucoplan	98
Table 68. Summary of UGT Inhibition by Zilucoplan	99
Table 69. Summary of Transporter Interaction of Zilucoplan and RA102758.....	100
Table 70. Summary of Zilucoplan PK Parameters, Single Ascending Dose Cohort (Study # UP0112)	101
Table 71. Summary of Zilucoplan PK Parameters, Multiple Dose Cohort (Study # UP0112)	102
Table 72. Metabolic Ratio of RA102758 and RA103488 Following the Final SC Administration of 0.2 mg/kg (QD) for 7 Days (Study # UP0112)	102
Table 73. Summary of Zilucoplan PK Parameters in Japanese and White Subjects, Single Dose Cohorts (Study # UP0113)	104
Table 74. Summary of Zilucoplan PK Parameters in Japanese and Caucasian Subjects, Multiple Dose Cohort (Study # UP0113).....	105
Table 75. Summary of RA102758 and RA103488 PK Parameters in Japanese and Caucasian Subjects, Single Dose Cohorts (Study # UP0113)	105

Table 76. Summary of RA102758 and RA103488 PK Parameters in Japanese and Caucasian Subjects, Multiple Dose Cohort (Study # UP0113)	106
Table 77. Summary of PK for Zilucoplan (RA101495) and Its Metabolites (RA102758 and RA103488) (Renal Impairment Study # UP0114).....	107
Table 78. Summary of Complement Component C5 Concentrations (Renal Impairment Study # UP0114)	107
Table 79. Statistical Assessment of Effect of Hepatic Impairment on Zilucoplan PK Parameters (Hepatic Impairment Study # UP0114).....	108
Table 80. Statistical Assessment of Effect of Hepatic Impairment on RA102758 PK Parameters (Hepatic Impairment Study # UP0114).....	109
Table 81. Statistical Assessment of Effect of Hepatic Impairment on RA103488 PK Parameters (Hepatic Impairment Study # UP0114).....	109
Table 82. Statistical Analysis of the Effect of Injection Sites on Zilucoplan Plasma PK Parameters (Relative Bioavailability Study # UP0115)	111
Table 83. Statistical Analysis of the Effect of Injection Sites on Zilucoplan PD (sRBC Lysis) Parameters (Relative Bioavailability Study # UP0115).....	111
Table 84. Summary of PK Bioanalytical Methods	112
Table 85. Summary of PD Bioanalytical Methods	113
Table 86. ADA Classification.....	117
Table 87. ADA Response and Incidence Rates (Study # MG0010, # MG0011)	117
Table 88. APA Response and Incidence Rates (Study # MG0010, # MG0011).....	118
Table 89. Summary of Study Designs With Zilucoplan Used in the Current Analysis...	123
Table 90. Baseline Characteristics of Zilucoplan PK Population in Study	124
Table 91. Final PopPK Model: Zilucoplan Parameter Estimates	129
Table 92. Analysis Data Sets	130
Table 93. Listing of Analyses Codes and Output Files	135
Table 94. Study MG0010: Shift Table for Subjects With Normal Baseline Serum Lipase by Treatment Group	139
Table 95. Study MG0010: Shift Table for Subjects With Normal Baseline Serum Lipase to Lipase >3xULN at Days 57 or 84, by Treatment Group	139
Table 96. Study MG0010-MG0011: Shift Table for Subjects With Normal Serum Lipase at Days 57 or 84 in MG0010 Compared to Serum Lipase at any Subsequent Visit in MG0011, by Original Treatment Group.....	140
Table 97. Study MG0009 DB Portion: Mean (95% CI) Serum Lipase at Days 1 and 84.....	142
Table 98. Study MG0009 DB: Shift Table for Subjects With Normal Baseline Serum Lipase by Treatment Group	142

Table 99. Key Labeling Changes and Considerations	144
Table 100. Covered Clinical Studies: MG0009 and MG0010.....	150
Table 101. Reviewers of Integrated Assessment	151
Table 102. Additional Reviewers of Application	152
Table 103. Signatures of Reviewers	153

Table of Figures

Figure 1. Mean sRBC Lysis (%) -Time Profile for 0.1 mg/kg and 0.3 mg/kg Doses From Phase 2 Study, MG0009.....	23
Figure 2. Mean Total C5 Concentration-Time Profile for 0.1 mg/kg and 0.3 mg/kg Doses From Phase 2 Study, MG0009	23
Figure 3. Subject 164-241 With GGT >10 x ULN (Copied from Applicant's Narratives pdf Document).....	53
Figure 4. Predicted Average Steady State Zilucoplan Concentration by Weight.....	66
Figure 5. Study Schematic (Study # UP0115)	110
Figure 6. Zilucoplan Plasma Concentrations (Geometric Mean ($\pm$ 95% CI)) Over Time by Cumulative ADA Status (Study # MG0010)	119
Figure 7. Zilucoplan Plasma Concentrations (Geometric Mean ($\pm$ 95% CI)) Over Time by Cumulative APA Status (Study # MG0010).....	119
Figure 8. Mean sRBC Lysis ($\pm$ 95% CI) Over Time by Cumulative ADA Status (Study # MG0010)	120
Figure 9. Mean sRBC Lysis ($\pm$ 95% CI) Over Time by Cumulative APA Status (Study # MG0010).....	120
Figure 10. Mean ($\pm$ 95% CI) Change From Baseline in MG-ADL Total Score Over Time by Cumulative ADA Status	121
Figure 11. Mean ($\pm$ 95% CI) Change From Baseline in MG-ADL Total Score Over Time by Cumulative APA Status.....	121
Figure 12. Forest Plot for Single Covariate Effects on Clearance With 95% CIs	125
Figure 13. Forest Plot for Single Covariate Effects on R _{max} With 95% CIs	126
Figure 14. Goodness-of-Fit Plots for the Final PopPK Model for Zilucoplan	127
Figure 15. pVPCs for Zilucoplan Stratified by Dose Using the Final PopPK Model (run110, Logarithmic Scale)	128
Figure 16. Distribution of Steady State Zilucoplan AUC by Weight Using the Final PopPK Model.....	130
Figure 17. Observed Zilucoplan Concentration Versus Time After First Dose by Dose and Study	131

Figure 18. Random Effects on Clearance and Volume of Distribution vs. Age, Sex and Race for PopPK Model With Only Weight Allometric Scaling	132
Figure 19. Simulated Steady State PK Profiles of Zilucoplan for the Proposed Weight-Based Dose Regimen Across Different Body Weight Groups	133
Figure 20. Simulated PK Exposure at Steady State Following Daily Proposed Weight-Based Dose Regimen of Zilucoplan Across Different Body Weight Groups	133
Figure 21. Mean (95%CI) of MG-ADL Score Change From Baseline by Time After Dose (mITT) From Study MG0010 by Weight Groups	134
Figure 22. Relationship Between Observed Concentration and Population Prediction Across Time Quantiles.....	135
Figure 23. Study MG0010: Mean (95% CI) Change in Serum Lipase Level by Visit and Treatment Group.	138
Figure 24. Study MG0010-0011: Long-Term Mean Serum Lipase (U/L) by Treatment Group and Week Since Randomization in MG0010	140
Figure 25. Study MG0009 DB and OLE: Mean Serum Lipase (U/L) by Randomization Group and Total Days in MG0009	141

Glossary

ACh	acetylcholine
AChR	acetylcholine receptor
ADA	antidrug antibodies
ADLB	Analysis Dataset of Laboratory values
AE	adverse event
APA	anti-PEG antibody
AUC	area under the concentration-time curve
C5	complement component 5
CFS	coronavirus disease of 2019-free set
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease of 2019
CYP	cytochrome P450
DB	double-blind
DDI	drug-drug interaction
DVTERM	protocol deviation term
ELISA	Enzyme Linked Immunosorbent Assay
EOS	end of study
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
gMG	generalized myasthenia gravis
IC ₅₀	half maximal inhibitory concentration
IND	investigational new drug
IR	information request
LSM	least squares mean
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	myasthenia gravis composite
MG-QOL15r	Revised Myasthenia Gravis Quality of Life 15-Item Scale
MH	medical history
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
NDA	new drug application
NONMEM	Nonlinear Mixed-Effects Modeling
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PBO	placebo
PD	pharmacodynamic
PEG	polyethylene glycol
PI	Prescribing Information
PK	pharmacokinetic

NDA 216834

Zilucoplan

PRO	patient-reported outcome
PT	preferred term
QC	quality control
QD	once daily
QMG	quantitative myasthenia gravis
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAS	Statistical Analysis System
SC	subcutaneous
SN	study number
SOC	system organ class
sRBC	sheep red blood cell
TE	treatment-emergent
TR	trial
TESAE	treatment-emergent serious adverse event
UGT	uridine diphosphoglucuronosyl transferase
ULN	upper limit of normal
USPI	United States Prescribing Information
ZLP	zilucoplan

I. Executive Summary

1. Summary of Regulatory Action

Union Chimique Belge (UCB) submitted a new drug application (NDA) 216834 for zilucoplan for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) positive. Zilucoplan is a macrocyclic peptide that functions as C5 complement inhibitor by blocking the cleavage of complement C5 to C5a and C5b and inhibiting the formation of membrane attack complex.

NDA 216834 was reviewed by a multidisciplinary review team that did not identify any issues that preclude approval. Each discipline has recommended approval. I, the signatory authority for this application, concur with those recommendations and agree that the benefit-risk assessment supports approval.

The Applicant submitted results from a single adequate and well-controlled study (Study MG0010), with confirmatory evidence from pharmacodynamic/mechanistic data, that provide substantial evidence of effectiveness of zilucoplan for the indication which supports approval for the treatment of adults with gMG who are anti-AChR-positive.

Study MG0010 was a double-blind, placebo-controlled, multicenter study that provided reliable and highly statistically significant ($p < 0.001$) evidence of an important patient-reported impact and clinical benefit on daily function on an acceptable primary outcome (i.e., change from baseline to week 12 on the Myasthenia Gravis-Specific Activities of Daily Living [MG-ADL]). Efficacy was further supported by a highly statistically significant result ($p < 0.001$) on a secondary endpoint using a validated direct physician assessment of motor function in subjects with gMG (change from baseline on the Quantitative Myasthenia Gravis [QMG] score). Supplementary analyses supported the primary and secondary results. Overall, the highly persuasive results on a clinically meaningful endpoint, with support on the secondary endpoint of QMG and multiple supplementary analyses, make reliance on a single efficacy study in this rare disease, with confirmatory evidence from relevant pharmacodynamic/mechanistic data, appropriate to support approval.

The available safety data show that risks of zilucoplan are acceptable for its intended use. I concur that identified risks can be mitigated through the proposed risk evaluation and mitigation strategy (REMS), product labeling, and be can further evaluated during routine and enhanced pharmacovigilance. The overall benefit-risk is favorable as described in the benefit-risk framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document and the product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Myasthenia gravis (MG) is a rare autoimmune disease affecting the neuromuscular junction. Abnormalities at the neuromuscular junction result in muscular weakness. At disease onset, some patients experience isolated ptosis and diplopia known as ocular myasthenia gravis. Patients with generalized myasthenia gravis (gMG) experience weakness in other distributions such as bulbar, axial, limb, and respiratory muscles. This weakness can affect activities of daily living and may affect respiration. The disease course is variable, with some patients experiencing prolonged remission while others may experience many emergency room visits. - MG is caused by antibodies that bind to functional proteins at the neuromuscular junction. A large majority of patients have detectable antibodies against the acetylcholine receptor (AChR; 80% of patients), whereas less than 10% of patients have antibodies against muscle specific kinase (MuSK). Antibodies are not detected in 10 to 15% of patients. - The diagnosis of MG is based on the clinical presentation, the presence of autoantibodies (anti-AChR, anti-MuSK, and others), and neurophysiological tests such as repetitive nerve stimulation and single-fiber electromyography.	MG is a rare, serious, life-threatening disease that can cause disability due to muscle weakness and death due to respiratory failure. Different autoantibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• There are several FDA-approved drugs for gMG—pyridostigmine, eculizumab (SOLIRIS), ravulizumab (ULTOMIRIS), efgartigimod (VYVGART), and rozanolixizumab (RYSTIGGO). • Pyridostigmine is administered as needed, and is sufficient treatment for some patients. Adverse effects of pyridostigmine are secondary to acetylcholine (ACh) accumulation at muscarinic receptors in smooth muscle and autonomic glands, and at nicotinic receptors in skeletal muscle. Adverse effects include muscular weakness, gastrointestinal side effects (common), and excess bronchial and oral secretions that can be a serious problem in certain patients. • Immunosuppressive treatments such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, and plasmapheresis and intravenous immunoglobulin (IVIg) are used off-label. • The biologic C5 inhibitors (eculizumab and ravulizumab) are FDA approved to treat AChR-positive gMG. These products have a warning and REMS for infections with encapsulated organisms including <i>Neisseria meningitidis</i> and other species. • Efgartigimod, a neonatal Fc receptor blocker, is indicated in AChR-positive gMG. Rozanolixizumab is also a neonatal Fc receptor blocker, and is indicated for the treatment of AChR-positive and MuSK-positive gMG. • Short-term rescue treatments for gMG include plasma exchange and intravenous immune globulin. Thymectomy is indicated for all patients with thymoma and for those with nonthymomatous generalized AChR-positive MG.	Despite currently available therapies, there remains a significant unmet clinical need for effective treatments for MG because not all patients with MG are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Corticosteroids, broadly recognized as a mainstay therapy for MG have a rapid action, are inexpensive, and usually result in benefit to patients with MG. However, patients often develop intolerable side effects. Nonsteroidal immunosuppressant treatments may have a delayed response and significant side effects. Many patients have inadequate response to steroids and nonsteroidal immunosuppressant treatment, with persistent and disabling muscle weakness, and disease relapses which may progress to MG crisis. Plasma exchange and intravenous immunoglobulin (IVIg) are used in patients with acute severe MG as their effect is rapid but short-lived.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- Study MG0010 was a Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, 12-week trial of the 0.3 mg/kg daily dose versus placebo in 174 subjects with AChR-positive gMG. The primary endpoint was change from baseline in total Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) score (8-item provider-administered PRO measure with each item scored 0 to 3, and higher scores indicate more severe symptoms). After 12 weeks of treatment, the between-groups difference in MG-ADL score was -2.09 points ($p < 0.001$) in favor of zilucoplan. For the secondary endpoint, Quantitative Myasthenia Gravis (QMG) score, the difference was -2.94 points ($p < 0.001$) in favor of zilucoplan. The other secondary endpoints (MGC and MG-QOL15r) were consistent with the primary endpoint result. - Study MG0009 was Phase 2, double-blind, placebo-controlled, 12-week trial in 44 subjects with AChR-positive gMG who were randomized (1:1:1) to placebo, 0.1 mg/kg, or 0.3 mg/kg. The primary endpoint was the between-groups difference in change from baseline to 12 weeks in QMG score (13-item validated physician-reported outcome measure with each item graded 0 to 3, and higher scores indicate greater weakness). The primary endpoint trended in favor of zilucoplan. - This small molecule C5 inhibitor has a similar mechanism of action as the biologics eculizumab and ravulizumab, which have shown clinical efficacy in the gMG population.	Study MG0010, a 12-week randomized double-blind, placebo-controlled study of zilucoplan provided reliable and statistically persuasive evidence that zilucoplan can help patients with anti-AChR antibody positive gMG achieve a clinically meaningful improvement in the symptoms of the disease that affect their activities of daily living, motor function, and disease severity. The potential role of zilucoplan for the treatment of patients with anti-MuSK gMG, seronegative gMG, and those with purely ocular MG is unclear because these patients were not evaluated in the clinical studies included in this BLA submission.

NDA 216834
Zilucoplan

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- There were 213 subjects with gMG and anti-AChR-positive who were exposed to any dose of zilucoplan. Total exposure (as of datalock) was 254 pt-yrs (329 pt-yrs including 120-day update) for the 0.3 mg/kg zilucoplan dose. A total of 131 subjects with gMG had at least 12 months of exposure to the 0.3 mg/kg zilucoplan dose, including the 120-day update. - The approved C5 inhibitors have a boxed warning and a REMS regarding the risk of meningococcal infection. This adverse event did not occur in the studies of zilucoplan (330 pt-yrs on 0.3 mg/kg) likely due to the small population size and short trial duration. However, a boxed warning will be included in the product labeling for zilucoplan as this risk is a class effect due to the mechanism of action of the drug. - Elevations in pancreatic enzymes and microscopic changes in the pancreas (acinar cell degeneration, fibrosis/fibroplasia, duct degeneration/regeneration, inflammatory cell infiltration) were consistent findings in the toxicity studies conducted in cynomolgus monkeys. - Pancreatitis occurred in the long-term human studies at a higher incidence than in the general population. Pancreatic cysts/pseudocysts with or without infection also occurred. There were two deaths from pancreatic adenocarcinoma. Patients and physicians should be informed of the risk of pancreatitis and other pancreatic conditions while on zilucoplan, which may be life-threatening.	As with the other C5 inhibitors, the risk of meningococcal infections will be addressed in labeling and mitigated through a REMS with recommendations for vaccination and antibiotic prophylaxis. There was also a safety signal identified for exocrine pancreas-related events for zilucoplan. This risk can be appropriately mitigated through labeling and monitored with enhanced pharmacovigilance.

Abbreviations: Ach = acetylcholine; AChR = acetylcholine receptor; gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; PRO = patient recorded outcome; QMG = quantitative myasthenia gravis; REMS = Risk Evaluation and Mitigation Strategy

2.2. Conclusions Regarding Benefit-Risk

Myasthenia gravis (MG) is a serious, life-threatening disease that can result in significant morbidity and mortality. Although there are several treatments approved to treat patients with generalized MG (gMG) (i.e., not purely ocular MG), there remains a need for effective treatments because not all patients with gMG are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Currently, there are two FDA-approved complement component 5 (C5) inhibitors (eculizumab and ravulizumab) for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody positive. There are two FDA-approved neonatal Fc receptor blockers (efgartigimod and rozanolixizumab). Efgartigimod is approved for intravenous administration and efgartigimod with hyaluronidase is approved for subcutaneous administration for the treatment of adult patients with gMG who are AChR-antibody positive. Rozanolixizumab is approved for the treatment of gMG in adult patients who are AChR or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

The Applicant has demonstrated the efficacy of zilucoplan for the treatment of adults with gMG who are anti-AChR-antibody positive in study MG0010. This study was a randomized double-blind, placebo-controlled, multicenter study that enrolled 200 subjects with gMG who were on stable dose of acetylcholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressive drugs. Subjects received 12 weeks of daily subcutaneous zilucoplan at a dose of 0.3 mg/kg (based on a bodyweight dosing table) or matching placebo. The primary efficacy endpoint was the between-groups difference in change in Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) total score (patient-reported outcome [PRO]) between baseline and week 12. The key secondary endpoints were Quantitative Myasthenia Gravis (QMG), myasthenia gravis composite (MGC), and Revised Myasthenia Gravis Quality of Life 15-Item Scale (MG-QOL15r). The Applicant assessed the between-groups difference in change from baseline to Week 12. This primary (MG-ADL) and secondary endpoint (QMG) have been used previously to support the approvals of efgartigimod, ravulizumab, eculizumab, and rozanolixizumab.

The Applicant has demonstrated a statistically significant and clinically meaningful effect on the primary and key secondary endpoints. There was an improvement (decrease) in the MG-ADL total score by 4.39 points (least squares mean [LSM] estimate) in the zilucoplan group as compared to 2.3 points in the placebo group ($p < 0.001$). Efficacy was supported by consistent directional changes in the key secondary endpoints, where QMG score decreased (improved) over 12 weeks by 6.19 points as compared to 3.25 points for placebo ($p < 0.001$). MGC and MG-QOL15r also showed similar trends in favor of zilucoplan.

The Applicant seeks an indication for the treatment of adults with gMG who are AChR-antibody positive. Study MG0010 was an adequate and well-controlled, multicenter study that provided reliable and persuasive evidence that zilucoplan benefited adult patients with gMG who were anti-AChR-antibody positive to achieve a clinically meaningful improvement in the symptoms of MG that affect their activities of daily living. Consistent and distinct treatment effects on MG-ADL and QMG confirm that the observed treatment differences between zilucoplan and placebo were clinically and statistically meaningful.

Study MG0010 was relatively large, given the size of the patient population. No single site provided an unusually large proportion of subjects, and no site was disproportionately

responsible for the observed treatment effect. These findings were statistically robust to sensitivity analyses and were generalizable across demographic subgroups of age, sex, body weight, and region of the world.

Additionally, pharmacodynamic and mechanistic data relevant to the pathophysiology of MG—increased mean total C5 levels (due to prolongation of half-life of zilucoplan-bound C5 rather than free C5) in the zilucoplan group as compared to no change in the placebo group—provide confirmatory evidence of near complete inhibition of C5 to support approval. Therefore, study MG0010 is capable of serving as a single adequate and well-controlled clinical study plus confirmatory evidence to establish substantial evidence of effectiveness of zilucoplan treatment in adult patients with gMG who are AChR-antibody positive.

The safety database for zilucoplan was adequate for the intended population and proposed dosing regimen. The safety database for gMG consisted of three studies—MG0009 (double-blind followed by an extension phase), MG0010 (double-blind only), and MG0011 (long-term extension of MG0009 and MG0010). At the 0.3 mg/kg zilucoplan dose level, 131 subjects with gMG were exposed for at least one year, including the 120-day update. Common adverse events included injection site reactions, upper respiratory tract infection, urinary tract infection, diarrhea, nausea, vomiting, and increased lipase and amylase.

Pancreatitis and other effects of zilucoplan such as pancreatic cysts and pseudocysts with and without infection were seen in the human studies of zilucoplan. This was consistent with the histologic findings and lipase (and amylase) elevations seen in the nonclinical studies. Additionally, two subjects died two months after diagnosis of advanced pancreatic adenocarcinoma (1 with history of pancreatitis and the other without).

These safety findings can be adequately addressed through labeling and through routine and enhanced pharmacovigilance and a REMS. Warning and Precautions statements will include serious meningococcal infection, other infection with encapsulated bacteria, and pancreatitis and other pancreatic conditions. Enhanced pharmacovigilance will be requested for serious adverse events related to infections, including meningococcal infection and opportunistic infection, and pancreatic conditions. A pregnancy outcomes study and a lactation study will be required as postmarketing requirements.

Based on the review of all available efficacy and safety data, the benefits of zilucoplan outweigh the risks for the treatment of adult patients with gMG who are AChR-antibody positive. The availability of zilucoplan will provide a new and effective treatment option via daily subcutaneous injections of this C5 inhibitor.

II. Interdisciplinary Assessment

3. Introduction

Myasthenia gravis is a rare antibody-mediated autoimmune neuromuscular disease. Patients with myasthenia gravis can be classified according to clinical features of the disease. Approximately two-thirds of patients will present with diplopia and ptosis and other symptoms restricted to the ocular muscles, referred to as ocular myasthenia gravis. Patients with generalized myasthenia gravis (gMG) experience weakness in other distributions such as bulbar, axial, limb, and respiratory muscles. Most patients with gMG have detectable antibodies against the acetylcholine receptor (AChR).

There are several FDA-approved drugs for gMG — pyridostigmine, eculizumab, ravulizumab, efgartigimod, and rozanolixizumab. Other options include immunosuppressive treatment (off-label) such as steroids and nonsteroidal immunosuppressants, and plasma exchange or intravenous immunoglobulin therapy (also off-label). However, patients often experience intolerable side effects. Up to 30% of patients have inadequate response to steroids and nonsteroidal immunosuppressant treatment, with persistent and disabling muscle weakness. There remains a significant unmet clinical need for effective treatments for gMG because not all patients are able to receive, tolerate, or adequately benefit from the available clinical treatments.

Zilucoplan is an inhibitor of complement C5-convertase that prevents the generation of anaphylatoxin C5a and the membrane attack complex. There are two approved C5 inhibitors for the treatment of gMG. Unlike zilucoplan, which is a peptide, these approved C5 inhibitors are monoclonal antibodies.

The proposed dosing regimen of zilucoplan is subcutaneous once daily dose of 0.3 mg/kg, which is supplied as prefilled syringes of various colors according to the dose provided. The proposed dosing, and that used in the studies, was according to bodyweight —16.6 mg (43 kg to <56 kg; rubine red), 23.0 mg (56 to <77 kg; orange), and 32.4 mg (77 to <150 kg; dark blue).

The Applicant seeks approval of zilucoplan for the treatment of adults with acetylcholine receptor antibody positive generalized myasthenia gravis. The Applicant has submitted the results of study MG0010 in support of the application. Study MG0010 was a 12-week, randomized (1:1), double-blind, placebo-controlled study designed to demonstrate superiority of zilucoplan 0.3 mg/kg in a population of 174 subjects with AChR-positive gMG. The Applicant also submitted the results of a Phase 2 study, MG0009 with a similar design. Study MG0009 included 44 subjects randomized (1:1:1) into 3 dose arms (zilucoplan 0.1 mg/kg, 0.3mg/kg, or placebo), followed by an extension phase. Subjects from both studies continued treatment in an open-label extension, study MG0011.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

Not applicable.

3.1.2. Key Safety Review Issues

The key safety review issues for this application are meningococcal infection (a class effect of the C5 inhibitors), other serious infections, and pancreatitis, which was seen in the human as well as nonclinical studies.

3.1.2.1. Pancreatitis and Associated Pancreatic Conditions

Pancreatitis and other effects of zilucoplan on the exocrine pancreas were seen in the human studies of zilucoplan. This was consistent with the histologic findings and lipase (and amylase) elevations seen in the nonclinical studies.

Seven subjects experienced pancreatic adverse events (four pancreatitis and multiple pancreatic cysts) in the extension phases. Five of these seven subjects had no prior pancreatic history. There were two deaths from pancreatic cancer. One subject who died from pancreatic cancer had a history of a previous pancreatic condition and the other did not.

Adverse events of elevated lipase and amylase were also noted in the clinical studies. There were no dose-modification criteria in these protocols for pancreatic events, despite lipase levels being scheduled lab tests in these studies due to the nonclinical findings of increased lipase. There was no requirement for baseline pancreatic ultrasound. Consequently, a few investigators considered pancreatic events related to zilucoplan, but most did not. This led to variability in discontinuation of zilucoplan due to pancreatic events. No subjects with pancreatic adverse events had zilucoplan discontinued permanently (except the two subjects who died shortly after the diagnosis of pancreatic cancer), and most subjects had zilucoplan continued through their pancreatic episodes.

Refer to Section [7.7.1](#) for further details.

3.1.2.2. Meningococcal Infection

Patients treated with complement inhibitors are at increased risk of *Neisseria* infections, particularly *Neisseria meningitidis*. The currently approved products have a boxed warning and a REMS to mitigate this risk.

No meningococcal infections were reported in the submitted studies of zilucoplan. However, the studies were of relatively small size and short duration. Subjects were required by protocol to have been vaccinated. Refer to Section [7.7.2](#) for further details.

3.1.2.3. Other Serious Infections

Refer to Section [7.7.3](#) for further details.

3.2. Approach to the Clinical Review

[Table 3](#) provides an overview of the clinical studies conducted to support the benefit-risk assessment of zilucoplan. Results from Phase 3 study MG0010 provide the primary basis for efficacy and safety assessment, augmented by the Phase 2 dose-ranging study MG0009 and long-term open-label study MG0011.

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety for Zilucoplan

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
MG0010 or RA101495-02.301 / NCT04115293	Adults with AChR-positive gMG	Control type: PC Randomization: 1:1 Blinding: double-blind Biomarkers: N/A Innovative design features: N/A	Drug: zilucoplan Dosage: 0.3 mg/kg/d Number treated: 86 zilucoplan, 88 PBO Duration (quantity and units): 12 wk	Primary: change from baseline MG-ADL Secondary: QMG, MGC, MG-QoL15r	156 planned, 174 enrolled	68 sites, 10 countries
MG0009 or RA101495-02.201 / NCT04115293	Adults with AChR-positive gMG	Control type: PC Randomization: 1:1:1 Blinding: double-blind Biomarkers: N/A Innovative design features: N/A	Drug: zilucoplan Dosage: 0.1 mg/kg/d or 0.3 mg/kg/d Number treated: 14 received low dose zilucoplan, 15 received high dose zilucoplan Duration (quantity and units): 12 wk	Primary: change from baseline in QMG Secondary: MG-ADL, QMG, MG-QoL15r	36 planned, 44 enrolled	22 sites, 2 countries
MG0011 or RA101495-02.302 / NCT04225871	Adults with AChR-positive gMG who were in MG0009 or MG0010	Control type: OLE Randomization: N/A Blinding: N/A Biomarkers: N/A Innovative design features: N/A	Drug: zilucoplan Dosage: 0.3 mg/kg/d Number treated: anticipated enrollment from MG0009 and MG0010 is approximately 200 Duration (quantity and units): ongoing, anticipated length is 2 y	Primary: safety/tolerability (TEAEs) Secondary: efficacy (MG-ADL, QMG, MGC, MG-QoL15r)	Rollovers from MG0009 and MG0010	63 sites, 10 countries

Source: Reviewer. CSR for MG0009, MG0010, MG0011

Abbreviations: AChR = acetylcholine receptor; gMG = generalized myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = myasthenia gravis composite; OLE = open-label long-term extension; QMG = quantitative myasthenia gravis.

4. Patient Experience Data

These data comprised the primary and key secondary endpoints.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	6.2.2.3 15.1
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Zilucoplan is a complement inhibitor, which acts by binding to complement component C5 to inhibit its cleavage to C5a and C5b and thereby inhibiting the formation of the membrane attack complex (MAC, terminal complement complex C5b-9). MAC is thought to mediate tissue damage at the neuromuscular junction in patients with AChR-ab positive myasthenia gravis.

In vitro pharmacology studies demonstrated potent binding of zilucoplan to human complement C5 protein and inhibition of C5 cleavage. In a functional assay, it was shown that binding to C5 and inhibition of C5 cleavage by zilucoplan blocked red blood cell lysis. An in vitro study

examining inhibition of complement-mediated hemolysis by zilucoplan showed that potency in the cynomolgus monkey (IC₅₀ 4 nM) was comparable to that in humans (IC₅₀ 7 nM) but much reduced in rat (609 nM) and other species (dog >4700 nM, mouse >36,000 nM, rabbit >67,000 nM, and guinea pig >100,000 nM). In vivo pharmacology studies in cynomolgus monkeys showed that plasma drug levels ≥ 2.5 µg/mL produced >90% inhibition of hemolysis. In the repeated-dose toxicity studies in monkey, nearly complete inhibition of hemolysis was demonstrated throughout the dosing period with recovery after dosing cessation.

5.2. Clinical Pharmacology / Pharmacokinetics

The clinical pharmacology program supporting the marketing application of zilucoplan for gMG indication included a total of nine studies. Six of the studies were Phase 1 studies ([Table 5](#)) in healthy volunteers characterizing pharmacokinetic (PK) and pharmacodynamic (PD) [total C5 levels, and complement inhibition as measured by sheep red blood cell (sRBC) lysis] of zilucoplan and evaluating the impact of intrinsic and extrinsic factors (Section [8.1](#) and [8.2](#)). Three of the studies are Phase 2 study (MG0009) and two Phase 3 studies (MG0010 and MG0011 [open-label extension of MG0009 and MG0010]) in gMG subjects in which PK and PD data of zilucoplan were collected. The major clinical pharmacology review focus is the assessment of the mechanistic evidence based on PD endpoint data (total C5 levels and complement inhibition) in gMG subjects (Phase 2 and 3 studies; Section [6.1.2](#)) and the assessment of the proposed body weight-band based dosing for zilucoplan (Section [8.1.4](#)).

Table 5. Phase 1 Clinical Pharmacology Studies in Healthy Volunteers

Study Number	Study
UP0112	Single Ascending Dose (SAD) and Multiple Dose (MD) Study
UP0113	Ethno-Bridging Study in Japanese and Caucasian Subjects
UP0114	Renal Impairment Study
UP0093	Thorough-QT (TQT) Study
UP0094	Hepatic Impairment Study
UP0115	Relative Bioavailability (BA) Study for Injection Sites

Source: Reviewer Generated Table

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Zilucoplan is 15-amino acid macrocyclic peptide that is a complement component 5 (C5) inhibitor.
Mechanism of action	Zilucoplan inhibits the effects of C5 through a dual mechanism of action. Specifically, zilucoplan binds with high affinity to C5 and inhibits its cleavage by the C5 convertase to C5a and C5b, which results into 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.
Active moieties	Zilucoplan
QT prolongation	Based on a thorough-QT study (TQT study, # UP0093) conducted to evaluate the effects of supratherapeutic zilucoplan plasma concentrations on the heart rate (HR)-QTc interval, at two times the recommended dose (i.e., 2x0.3 mg/kg =0.6 mg/kg), zilucoplan does not prolong the QT interval to any clinically relevant extent. The mean (upper 90% confidence interval) QTcF increase was 3.2 milliseconds (5.3 milliseconds).
	General Information
Bioanalysis	The plasma, urine, and feces concentration of zilucoplan and metabolites were determined by validated liquid chromatography-mass spectrometry (LC/MS/MS) methods. The total C5 levels and complement inhibition were measured by validated enzyme-linked immunosorbent assay (ELISA) and sheep red blood cell (sRBC) lysis assay respectively. Refer to Section 14.3 for further details.
Healthy subjects versus patients	Based on population pharmacokinetic (PK) analysis, zilucoplan PK is similar in healthy subjects and subjects with gMG.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	From Phase 3 study, MG0010, that dosed 0.3 mg/kg zilucoplan once daily for 12-weeks, mean (SD) C _{trough} (ng/mL) were reported to be 12846.9 (2805.3).
Range of effective dose(s) or exposure	A zilucoplan dose of 0.3 mg/kg administered subcutaneously once daily was studied in Phase 3 study (Study # MG0010) that resulted in complement inhibition of 97.5% observed by the end of the first week and sustained throughout the 12-week treatment period.
Maximally tolerated dose or exposure	The highest evaluated dose in humans was 0.6 mg/kg (once daily for 7 days) in adult healthy subjects (n=32) (TQT study, # UP0093)
Dose proportionality	Zilucoplan peak exposure (C _{max}) was approximately dose-proportional while the increase in zilucoplan. Systemic exposure (AUC _{0-inf}) was less than dose-proportional when administered as a single dose in the range of 0.05 mg/kg to 0.4 mg/kg (Study # UP0112).

NDA 216834
Zilucoplan

Characteristic	Drug Information
Accumulation	Following daily subcutaneous dosing of zilucoplan, 0.3 mg/kg, for 14 days in healthy subjects, both C _{max} and AUC _{tau} increased by approximately 3-fold (Study # UP0113)
Time to achieve steady-state	Steady-state exposures of zilucoplan was achieved by week 4 and remained stable through Week 12 following zilucoplan once daily dose of 0.3 mg/kg for 12 weeks in gMG subjects (Study # MG0010)
Bridge between to-be-marketed and clinical trial/study formulations	To-be-marketed product in three dose presentations (16.6 mg/0.416 mL, 23 mg/0.574mL, 32.4 mg/0.810mL) is a sterile, preservative-free solution (40 mg/mL) in a single-use prefilled syringe placed into a safety syringe device and was also used in Phase 2 and Phase 3 clinical studies. There was no change in the formulation in the clinical development program of zilucoplan. For Phase 1 study # UP0112, zilucoplan formulation was filled in glass vial. Overall, any bridging study is not required.
Absorption	
Bioavailability	Absolute or relative bioavailability of zilucoplan in humans in not studied.
T _{max}	3 – 6 hours (Median)
Food effect (fed/fasted) Geometric least square mean and 90% CI	Zilucoplan is administered by subcutaneous injection, and therefore food-effect is not relevant.
Distribution	
Volume of distribution	Based on population PK analyses, the mean estimate of volume of distribution at steady state was 3.51 L
Plasma protein binding	>99% protein binding for zilucoplan and its two metabolites, RA102758 and RA103488.
Drug as substrate of transporters	Zilucoplan is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3. The substrate potential of zilucoplan for renal transporters (OAT1, OAT3, MATE1/MATE2-K, OCT2) is not evaluated. It is noted that excretion of zilucoplan and its metabolites is negligible (<1% of the dose) and hence the lack of these data are not concerning.
Elimination	
Mass balance results	No dedicated mass balance study was conducted. In renal impairment study (# UP0114) at a single dose of 0.3 mg/kg, zilucoplan and its metabolites are minimally excreted in urine in both the normal and severe renal impairment subjects (<1% of dose in total across all analytes). Based on the concentrations of zilucoplan in feces from hepatic impairment study (UP0094) at a single dose of 0.3 mg/kg, estimated fecal excretion of zilucoplan and its metabolites was negligible (<1% of dose) in both the normal and moderate hepatic impairment subjects.
Clearance	Based on population PK analyses, the mean estimate of clearance at steady state was 0.085 L/h
Half-life	Mean terminal half-life was 172 hours

Characteristic	Drug Information
Metabolic pathway(s)	As a peptide, zilucoplan is expected to be degraded into small peptides and amino acids via catabolic pathways. Two primary metabolites of zilucoplan detected in plasma are RA102758 and RA103488. The metabolite RA102758 is formed by protease mediated degradation of the c terminal lysine residue attached to the ethylene glycol-palmitoyl tail. The metabolite RA103488 is formed by ω-hydroxylation on the palmitoyl tail of intact zilucoplan majorly by CYP4F2 (minor contribution by CYP4A11, CYP4F3A, and CYP4F3B). Of the above two metabolites, RA103488 is pharmacologically active with IC₅₀ for %RBC lysis similar to that of zilucoplan (RA103488 – 5.5nM; Zilucoplan – 5.2nM). Based on study # UP0113 at zilucoplan dose of 0.3 mg/kg (once daily dose for 14 days), the exposure of above two metabolites is low compared to zilucoplan {RA102758 – 10.6% of zilucoplan exposure; RA103488 – 9.4% of zilucoplan exposure}. Due to the low exposure of metabolites, any contribution by active metabolite to overall pharmacological activity is therefore not substantial. In vitro studies did not suggest any contribution by transporters towards disposition of zilucoplan.
Primary excretion pathways (% dose)	Zilucoplan is a cyclic peptide and is expected to be degraded into small peptides and amino acids via catabolic pathways. Excretion of zilucoplan and its metabolite in urine and feces was negligible (<1% of the dose).
<i>Intrinsic Factors and Specific Populations</i>	
Body weight	Body weight-band based dosing regimen was evaluated throughout the clinical development program for zilucoplan. In Phase 3 study, MG0010, gMG subjects received 0.3 mg/kg once daily doses as per the weight-bands presented in Table 7 which is same as the originally proposed weight-band based dosing regimen. In response to FDA's labeling edits (updated label dated August 14, 2023, sent by email), the Applicant proposed to include patients weighing >150kg in the label (Table 8).

Table 7. Total Daily Dose by Body Weight Range in Phase 3 Study (MG0010)

Weight Range (kg)	Target Zilucoplan Dose (mg/kg)	Actual Zilucoplan Dose (mg)	Dose Range (mg/kg)
≥43 to <56	0.3	16.6	0.30 to 0.39
≥56 to <77	0.3	23	0.30 to 0.41
≥77 to 150	0.3	32.4	0.22 to 0.42

Source: Adapted from Table 3-1 from MG0010 Clinical Study Report

Table 8. Proposed Total Daily Dosage by Body Weight Range

Body Weight	Once Daily Dosage
Less than 56kg	16.6 mg
56kg to less than 77kg	23 mg
77kg and above	32.4 mg

Source: Adapted from Table 1 from Updated Label Received on August 14, 2023, sent by email

Characteristic	Drug Information
	Based on population PK analysis, it was confirmed that body weight is a significant covariate, and the simulation results further support body weight-band based dosing regimen. For details, refer Section 8.1.4 and 14.5.
Age	No age-based dose adjustments are needed. Population PK analyses of data from Phase 1, 2 and 3 studies indicated that age range from 20 to 76 years had no clinically significant impact on the pharmacokinetics of zilucoplan.
Sex	No sex-based dose adjustments are needed. Population PK analyses of data from Phase 1, 2 and 3 studies indicated that sex had no clinically significant impact on the pharmacokinetics of zilucoplan.
Race	No race-based dose adjustments are needed. Population PK analyses of data from Phase 1, 2 and 3 studies indicated that race had no clinically significant impact on the pharmacokinetics of zilucoplan.
Renal impairment	No dose adjustment is needed for patients with any degree of renal impairment based on the findings from clinical study (# UP0114) that compared zilucoplan PK in subjects with severe renal impairment and matched normal healthy subjects.
Hepatic impairment	No dose adjustment is needed in patients with mild or moderate hepatic impairment based on the findings from clinical study (# UP0094) that compared zilucoplan PK in subjects with mild and moderate hepatic impairment and matched normal healthy subjects. The pharmacokinetics of zilucoplan in patients with severe hepatic impairment have not been studied.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Zilucoplan and metabolite RA102758 do not inhibit CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP4F). Zilucoplan does not induce CYP enzymes (CYP1A2, CYP2B6, CYP3A4) and does not inhibit UGT (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15).
Inhibition/induction of transporter systems	Zilucoplan and metabolite RA102758 do not inhibit transporters (p-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2).
Immunogenicity (if Applicable)	
Bioanalysis	Immunogenicity assessments were conducted using direct immune binding assay to determine the exposures of antidrug antibodies (ADA) and anti-polyethylene glycol (PEG) antibodies (APA).
Incidence	In Phase 3 study # MG0010, in up to 12 weeks of treatment, up to 2.3% (2/86) and 9.3% (8/86) of subjects treated with zilucoplan developed antidrug antibodies and anti-PEG antibodies respectively.
Clinical impact	Because of the low occurrence of antidrug antibodies and anti-PEG antibodies, the available data are too limited to make definitive conclusions regarding immunogenicity and its effect on pharmacokinetics, pharmacodynamics, safety, or efficacy of zilucoplan.

Source: Reviewer Generated Table

Abbreviations: C5 = complement component 5; MAC = membrane attack complex; gMG = generalized myasthenia gravis; PK = pharmacokinetic; QTc = corrected QT; QTcF = QT corrected for heart rate by Fridericia's cube root formula; TQT – thorough-QT study; C_{max} = maximum plasma concentration or peak exposure; AUC_{0-inf} = area under the curve_{0-inf} or total systemic exposure; CYP = cytochrome P450; UGT = UDP glucuronosyl transferase; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; OATP1B1/1B3 = organic anion transporting polypeptide 1B1/1B3; OAT1/OAT3 = organic anion transporter 1/3; MATE1/MATE2-K = multidrug and toxin extrusion (MATE) proteins; OCT1/OCT2 = organic cation transporter 1/2; PEG = polyethylene glycol

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Assessment of Dose

For the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) antibody positive, the proposed dose for zilucoplan is 0.3 mg/kg once daily administered as a subcutaneous injection and is dependent on actual body weight range as presented in [Table 8](#). Each dose presentation in prefilled syringe provides a fixed dose of 16.6 mg, 23 mg, and 32.4 mg zilucoplan depending on body weight. The dosing regimen using weight brackets ([Table 7](#)) was evaluated in Phase 3 (MG0010) study in gMG subjects who are AChR-antibody positive. A body weight-band based dosing regimen was evaluated throughout the clinical development program for zilucoplan. In response to FDA's labeling edits (updated label dated August 14, 2023, sent by email), the Applicant proposed to include patients weighing >150kg in the label ([Table 8](#)). Specifically, the dosing for patients with weight >150kg is 32.4mg which is same as the dose that was proposed for patients in the weight range of 77kg-150kg and evaluated in Phase 3 study (MG0010). For further details on the Applicant's rationale to use the same dose for gMG patients with weight >150 kg as that of gMG patients with weight 77 kg to 150kg and its assessment are presented in Section [8.1.4](#).

The Applicant conducted a Phase 1 study (Study UP0112 – randomized, double-blind, placebo-controlled study) evaluating single doses (SD) of 0.05, 0.10, 0.20, and 0.40 mg/kg; and multiple doses (MD) of 0.2 mg/kg for 7 days by subcutaneous administration in adult healthy volunteers. PK and PD (total C5 levels; and complement inhibition [ex vivo %sRBC lysis or hemolysis]) were collected. The Applicant noted that across all dose groups, plasma levels of total C5 increased following a single dose and multiple doses. The mean maximum total C5 levels reached 81µg/mL, 99µg/mL, 99µg/mL, 116 µg/mL postdose following single doses of 0.05, 0.1, 0.20, and 0.40 mg/kg respectively. There were no notable changes observed in C5 concentration across the time points for the placebo groups. For MD cohort, 0.2 mg/kg for 7 days, the mean maximum total C5 levels reached 151µg/mL. The observed increase in C5 is due to the prolongation of the half-life of C5 bound to zilucoplan and not due to increase in available free C5. The Applicant noted that the increases in C5 level coincided with increased plasma level of zilucoplan.

For complement inhibition, the Applicant found that the mean maximum percent inhibition of sRBC lysis compared to baseline reached 52%, 86%, 87%, and 95% postdose following single doses of 0.05, 0.1, 0.20, and 0.40 mg/kg, respectively, suggesting dose-dependent complement inhibition. There was no inhibition of sRBC lysis for the pooled placebo group across all time points. For MD cohort, 0.2 mg/kg for 7 days, the mean percent inhibition of sRBC lysis reached >95% after first dosing and continued through the 7 days of dosing. It was also noted that the maximum %sRBC lysis inhibition i.e., peak PD effect coincided with the time for peak concentration (T_{max}) of zilucoplan for both single doses and multiple dose cohorts. The overall

PK and PD data from this Phase 1 study suggested correlation between PK and complement inhibition.

In the study UP0113 (ethnobridging study) at 0.3 mg/kg dose, after multiple administration (once daily for 14 days), at 24 hours post last dose, the increase in total C5 and the inhibition of %sRBC lysis in white subjects was approximately 64% and 95% respectively at steady state.

PK and PD and safety/tolerability information from the Phase 1 study UP0112 along with clinical experience of zilucoplan in Phase 2 studies for paroxysmal nocturnal hemoglobinuria (PNH) indication led to the selection of two doses, 0.1 mg/kg and 0.3 mg/kg, for Phase 2 study (MG0009) in gMG subjects. The weight-band based dosing was also used in this Phase 2 study ([Table 9](#)).

Table 9. Phase 2 (MG0009) and Phase 3 (MG0010) Zilucoplan Doses by Weight Brackets

Nominal Target Dose (mg/kg)	Actual Dose (mg)	Weight Range (kg)	Dose Range (mg/kg)
0.1 (MG0009 only)	6.0	≥ 43 to < 61	0.10 to 0.14
0.1 (MG0009 only)	8.8	≥ 61 to < 88	0.10 to 0.14
0.1 (MG0009 only)	12.4	≥ 88 to < 109	0.11 to 0.14
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 < 109 (MG0009) ≥77 to 150 (MG0010)	0.30 to 0.42 (MG0009) 0.22 to 0.42 (MG0010)

Source: Table 1-3 from Summary of Clinical Efficacy (Module 2.7.3)

The results from this Phase 2 study indicated that greater inhibition of complement pathway occurred with 0.3 mg/kg dose (94.9% inhibition at week 12) when compared with the 0.1 mg/kg dose (81.8% inhibition at week 12) ([Figure 1](#)). Further, the Applicant found that the dose of 0.3 mg/kg provided superior efficacy pertaining to the primary (QMG) and key secondary (MG-ADL) endpoints and similar safety profile compared to 0.1 mg/kg (refer to Section [15.1](#)). The dose-response for the clinical outcome measures is consistent with the dose-response for the complement inhibition when comparing 0.1 and 0.3 mg/kg dose groups.

Based on the above results from Phase 2 study, the Applicant selected 0.3 mg/kg dose for Phase 3 study (MG0010) that would provide near complete complement inhibition for therapeutic benefit. The weight-band based dosing implemented in Phase 3 study ([Table 9](#)) is the same as the proposed weight-band based dosing regimen ([Table 8](#)) except that the inclusion of gMG subjects with weight >150 kg is proposed for the labeling (Refer to Section [8.1.4](#)). In Phase 3 study, zilucoplan resulted in complement inhibition of 97.5% by the end of the first week and sustained throughout the 12-week treatment period. The efficacy and safety results for Phase 3 study are discussed in detail in Section [6.2.2](#).

The Applicant noted that once daily dosing interval is needed to maintain the exposure for complement inhibition and therapeutic benefit. PK simulations conducted by the Applicant indicated that longer dosing intervals cannot achieve adequate exposures and fail to maintain the depth of complement inhibition needed for maximum therapeutic benefit. The Applicant further noted that once every other day dosing is estimated to reduce the zilucoplan trough concentration

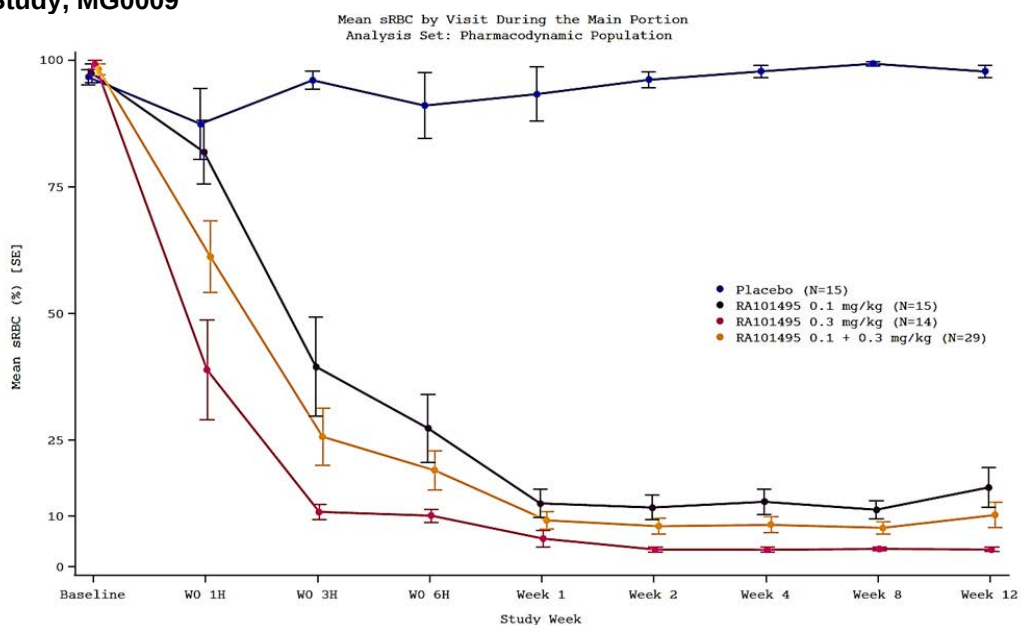
by approximately 50%, resulting in inadequate pharmacodynamic effect. Once daily dosing interval of zilucoplan was studied in both Phase 2 and Phase 3 studies.

In summary, based on the above, for the treatment of adult gMG patients who are anti-AChR-antibody positive, the Applicant proposed 0.3 mg/kg once daily subcutaneous dose with fixed dose for each weight range. The proposed weight-band based dosing regimen is further supported by the population PK analysis and simulation as discussed in Sections [8.1.4](#) and [14.5](#). The proposed weight-band based dosing regimen is acceptable. The assessment of the Applicant's proposal of the inclusion of gMG patients with weight greater than 150 kg in the labeling is presented in Section [8.1.4](#).

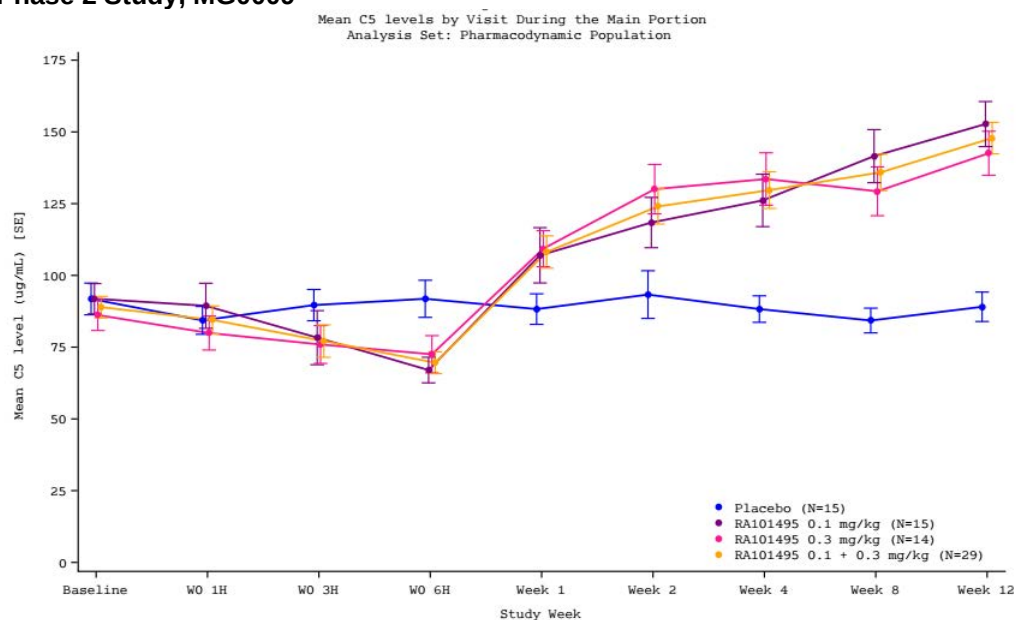
6.1.2. Mechanistic Evidence of Support

From the Phase 2 study, MG0009, that evaluated two doses, 0.1 mg/kg and 0.3 mg/kg, there was an increase in mean total C5 levels in zilucoplan dose groups at week 1; whereas there was no change in total C5 levels in the placebo group ([Figure 2](#)). Though the mean total C5 levels were similar across zilucoplan dose groups at each time point, both 0.1 mg/kg and 0.3 mg/kg dose groups were significantly separated from placebo group from week 1 onwards ([Figure 2](#); total C5 at week 12 for placebo, 0.1 mg/kg, and 0.3 mg/kg respectively 89.06 µg/mL, 152.73 µg/mL, 142.57 µg/mL). Similarly, in the Phase 3 study (MG0010) that evaluated dose of 0.3 mg/kg, the mean total C5 levels reached to 102.6 µg/mL at week 1 (total C5_{placebo} = 90.6 µg/mL) and 138.8 µg/mL at Week 12 (total C5_{placebo} = 91.3 µg/mL) and was consistent with that observed in Phase 2 study. No change was observed in the placebo group for the total C5 levels in Phase 3 study. The observed increase in C5 is due to the prolongation of the half-life of C5 bound to zilucoplan and not due to increase in available free C5. From the above PD data, it can be concluded that zilucoplan dose groups trended towards an increase in total C5 levels when compared to placebo. It is also noted that near complete complement inhibition observed with zilucoplan is consistent with that of the approved C5 inhibitors.

Overall, the data on the changes in total C5 levels relevant to the pathophysiology of gMG provide mechanistic evidence for zilucoplan and adds support to the effectiveness findings from Phase 3 study MG0010 for patients with gMG who are AChR-antibody positive.

Figure 1. Mean sRBC Lysis (%) -Time Profile for 0.1 mg/kg and 0.3 mg/kg Doses From Phase 2 Study, MG0009

Source: Figure 10-2 (Pg 273 of 297) and Figure 2.2.1 (Pg 19 of 20) from MG0009 Clinical Study Report
Abbreviations: sRBC = Sheep Red Blood Cell; SE = Standard Error; RA101495 = Zilucoplan

Figure 2. Mean Total C5 Concentration-Time Profile for 0.1 mg/kg and 0.3 mg/kg Doses From Phase 2 Study, MG0009

Source: Figure 10-3 (Pg 277 of 297) and Figure 2.2.2 (Pg 20 of 20) from MG0009 Clinical Study Report
Abbreviations: SE = Standard Error; RA101495 = Zilucoplan

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Results of Pooled Analyses

Not applicable.

6.2.2. Study MG0010

6.2.2.1. Design, Study MG0010

Overview and Objective

Study MG0010 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in 174 adults with gMG designed to demonstrate the efficacy of once-daily subcutaneous injections of zilucoplan. Subjects were randomly assigned (1:1) to 12 weeks of zilucoplan 0.3 mg/kg or placebo after stratification by baseline MG-ADL score (9 or less versus 10 or more), baseline QMG score (17 or less versus 18 or more), and geographical region (North America, Europe, East Asia). Subjects were expected to remain on stable doses of all other medications for MG unless otherwise medically indicated.

The primary efficacy endpoint was to evaluate the clinical efficacy of zilucoplan as assessed by the change from baseline on the MG-ADL score after 12 weeks of treatment with zilucoplan.

MG-ADL is an interviewer-administered patient-reported outcome that assesses eight signs and symptoms of MG. Each item is scored on a discrete 0- to 3-point scale (0=none, 1=mild, 2=moderate, and 3=severe). Individual item scores are added to give a total score that can range from 0 (no impairment) to 24 (severe impairment). The subject must not have received a cholinesterase inhibitor <10 hours prior to the MG-ADL assessment.

Secondary efficacy endpoints:

- Between-groups difference in QMG total score at week 12. QMG is a physician- or trained interviewer-administered PRO with 13 items assessing diplopia, ptosis, facial muscles, swallowing, and arm, head, and leg muscle function. Each item is scored on a discrete 0- to 3-point scale (0=none, 1=mild, 2=moderate, and 3=severe). Individual item scores are added to give a total score that can range from 0 (no impairment) to 39 (severe impairment).
- Between-groups difference in Myasthenia Gravis Composite (MGC) total score at Week 12. MGC is comprised of 10 items originating from other scales (i.e., QMG, MMT, MG-ADL). Each item is scored as an integer from 0 to 5. The total score can range from 0 (none) to 50 (severe).
- Between-groups difference in Myasthenia Gravis Quality of Life 15-item Scale – Revised (MG-QOL15r) total score at Week 12. This is a self-administered PRO designed to assess quality of life in MG. Each item is scored on a 0- to 2-point scale (0=not much at all, 1=somewhat, and 2=very much). The total score is the sum of the individual item scores, and ranges from 0 to 30.

Efficacy and safety assessments in this 3-month study were scheduled at screening (28 days before the baseline visit) then baseline (day 1) then weeks 1 (day 8), 2, 4, 8, 12 (day 84), and safety follow-up (6 to 7 weeks after last visit). Safety assessments included metabolic panel, and gamma-glutamyl transferase (GGT) and amylase and lipase levels, among others (hematology, coagulation, urine analysis and pregnancy test, 12-lead ECG, and physical exam).

Neisseria meningitidis vaccination was given as needed through the study per standard of care.

6.2.2.2. Eligibility Criteria, MG0010

The main eligibility criteria were as follows:

- Subjects 18 to <75 years of age
- Symptomatic gMG (MGFA Class II-IV)
- Positive test for AChR antibodies
- MG-ADL total score of 6 or more and a QMG total score of 12 or more (four or more of the QMG test items score at 2 or more)
- No change in baseline steroids or immunosuppressive therapy for at least 30 days prior to baseline
- Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to the first dose of study drug at the Day 1 visit. A booster vaccination should also be administered as clinically indicated, according to the local standard-of-care for subjects who have been previously vaccinated against *Neisseria meningitidis*
- At the time of QMG (but not MG-ADL) scoring, subjects must have been off acetylcholine inhibitor therapy for at least 10 hours
- Negative serum and urine pregnancy tests within 24 hours of first dose; and use of effective contraception during study and 40 days after discontinuation of drug

6.2.2.3. Statistical Analysis Plan, MG0010

Study MG0010 was a Phase 3, multicenter, randomized, double-blind (DB), placebo-control, parallel group study of subjects with gMG.

Approximately 156 subjects were planned (while 174 were enrolled) to be randomized with a ratio of 1:1 to the drug, or the placebo group, stratified by baseline MG-ADL score (≤ 9 versus ≥ 10) and region (North America, Europe, and East Asia). Roughly 78 subjects per group were expected to have about 94% power to detect a 2.3-point difference on the primary endpoint with standard deviation of 3.7 points. The source of the effect size appears to be based on the Phase 2 study MG0009. The rates of rescue and dropout were assumed to be up to 10% and 5% respectively.

The primary endpoint for this study was the change from the baseline in the MG-ADL (Myasthenia Gravis-Activities of Daily Living) score after twelve weeks of treatment during the 12-week, double-blind treatment period.

The MG-ADL is an 8-item questionnaire that focuses on relevant symptoms and functional performance of activities of daily living (ADL) in patients with MG. The 8 items of the MG-ADL questionnaire were derived from symptom-based components of the original 13-item QMG scale to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24. The recall period for MG-ADL is the preceding 7 days.

The three prespecified Family 1 secondary endpoints for this study were:

- Change from baseline to week 12 in QMG score
- Change from baseline to week 12 in MGC (Myasthenia Gravis Composite) score
- Change from baseline to week 12 in MG-QOL15r (Revised Myasthenia Gravis Quality of Life 15-item scale) Survey

The four prespecified Family 2 secondary endpoints for this study were:

- Proportion of subjects who received rescue therapy over the 12-week treatment period
- Proportion of subjects with MG-ADL score of 0 or 1 at week 12 without rescue therapy
- Proportion of subjects with ≥ 3 points reduction in MG-ADL score at week 12 without rescue therapy
- Proportion of subjects with ≥ 5 points reduction in QMG score at week 12 without rescue therapy

The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item); each graded 0 to 3, with 3 being the most severe. The range of total QMG score is 0 to 39.

The study design (double-blinded, randomized, placebo-controlled, parallel group) and the choice of the primary endpoint definition (change from baseline in MG-ADL score during the last week of the 12-week double-blind treatment period) were considered appropriate.

The primary endpoint was analyzed using a mixed effect repeated measures (MMRM) model that included treatment group, baseline MG-ADL score, baseline QMG score, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and baseline MG-ADL score-by-visit as fixed effects, using an unstructured correlation matrix; subjects were added as random effects in the model; weeks 1, 2, 4, 8, and 12 were included in the model.

Efficacy analyses were based on the modified intent-to-treat (mITT) population defined as all randomized subjects who received at least one dose of study drug grouped by randomized treatment group (for reporting efficacy data). Subjects were grouped based on the assigned treatment.

Any rescue therapy or MG crisis or death were considered as treatment failure, and any missing data due to these reasons were imputed using baseline or last value available, whichever was worse, i.e., worst observation carry forward (WOFCF).

Type 1 error was controlled by hierarchical testing. The primary endpoint was analyzed at the 0.05 level. If the primary endpoint were significant, the three Family 1 secondary endpoints would be analyzed at the 0.05 level in the prespecified sequence: QMG, MGC, MG-QOL15r.

If all endpoints in the Family 1 were significant at 2-sided type 1 error of 5%, Family 2 was tested using a Holm procedure at 2-sided type 1 error. The Holm procedure is a multistep, step-down procedure. The procedure started with the smallest p-value that was compared to 0.0125. If the first test showed statistical significance, the treatment effect for the respective endpoint was considered significant. Then, testing proceeded comparing the next smallest p-value to 0.017. If the second test showed statistical significance, testing proceeded comparing the third smallest p-value to 0.025. If the third test showed statistical significance, testing proceeded comparing the largest p-value to 0.05. The procedure stopped when a step yielded a nonsignificant result, i.e., once an ordered p-value was not significant, the remaining larger p-values were not evaluated.

6.2.2.4. Results of Analyses, Study MG0010

6.2.2.4.1. Subject Disposition, Demographic and Baseline Characteristics

This study enrolled the first subject on September 17, 2019, and last subject completed on December 30, 2021. The study report was created on June 30, 2022.

Of the 239 screened subjects, 63 subjects were screen failures, and two subjects withdrew consents before the randomization. In total, 174 subjects were randomized and treated (placebo: N=88; zilucoplan: N=86).

Overall discontinuation rates were low. Eight subjects (4.6%) did not complete the study. Demographic variables were balanced between treatment groups. Baseline medications for gMG were balanced between treatment groups and included cholinesterase inhibitors (85%), prednisone (41%), and other corticosteroids (22%).

Table 10. Subject Dispositions – Study MG0010

Subject Counts	Zilucoplan	Placebo	Total
Randomized	86	88	174
Treated	86	88	174
Completed	82	84	166

Source: Table 7-1 in the sponsor's study report, verified by the statistical reviewer.

There were two deaths in the double-blind period, one in the drug group and one in the placebo group. More detailed analyses about these two subjects are in the missing data and sensitivity analyses section.

Demographic variables were balanced across the drug and placebo groups.

Table 11. Subject Baseline Demographics – mITT – Study MG0010

Demographic	Zilucoplan 0.3 mg/ kg (N=86)	Placebo (N=88)	Total (N=174)
Age at Informed Consent (years)			
Mean (SD)	52.6 (14.6)	53.3 (15.7)	53.0 (15.1)
Median	54.5	55.5	55.0
Minimum, Maximum	21, 75	19, 75	19, 75
Age Group, n (%)			
18 to 65 years	64 (74.4)	62 (70.5)	126 (72.4)
65+ years	23 (25.6)	26 (29.5)	48 (27.6)
Gender, n (%)			
Female	52 (60.5)	47 (53.4)	99 (56.9)
Male	34 (39.5)	41 (46.6)	75 (43.1)
Race, n (%)			
American Indian or Alaska Native	0	1 (1.1)	1 (0.6)
Asian	7 (8.1)	14 (15.9)	21 (12.1)
Black	6 (7.0)	7 (8.0)	13 (7.5)
Native Hawaiian or Other Pacific Islander	0	0	0
White	66 (76.7)	62 (70.5)	128 (73.6)
Other/Mixed	0	0	0
Missing	7 (8.1)	4 (4.5)	11 (6.3)
BMI (kg/m ²)			
Mean (SD)	31.4 (7.22)	30.5 (8.02)	31.0 (7.63)
Median	30.5	29.0	30.0
Minimum, Maximum	19, 50	16, 54	16, 54
Weight Category, n (%)			
<56 kg	5 (5.8)	6 (6.8)	11 (6.3)
≥56 to <77 kg	21 (24.4)	25 (28.4)	46 (26.4)
≥77 to <150 kg	60 (69.8)	54 (61.4)	114 (65.5)
≥150 kg	0	3	3 (1.7)
Region, n (%)			
East Asia	7 (8.1)	9 (10.2)	16 (9.2)
Europe	34 (39.5)	33 (37.5)	67 (38.5)
North America	45 (52.3)	46 (52.3)	91 (52.3)

(Source: modified from the Table 7-4 in the sponsor's study report, verified by the statistical reviewer.)

Note: Due to local regulations in France, race was not recorded.

Baseline disease characteristics were consistent with a gMG population and balanced across the treatment groups.

Abbreviations: BMI = body mass index; mITT = modified intent-to-treat

Table 12. Subject Baseline Disease Characteristics – mITT – Study MG0010.

Characteristic	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)	Total (N=174)
Age at MG Onset (Years)			
n	85	88	173
Mean (SD)	43.47 (17.35)	44.02 (18.67)	43.75 (17.98)
Median	43.0	44.5	44.0
Min, Max	13.0, 73.0	9.0, 73.0	9.0, 73.0
Duration of MG (Years)			
Mean (SD)	9.34 (9.47)	8.96 (10.43)	9.15 (9.94)
Median	5.55	4.75	5.00
Min, Max	0.1, 42.3	0.2, 51.9	0.1, 51.9
Symptoms at Onset, n (%)			
Ocular	28 (32.6)	34 (38.6)	62 (35.6)
Generalized	58 (67.4)	54 (61.4)	112 (64.4)
MG-ADL total score at baseline			
Mean (SD)	10.3 (2.5)	10.9 (3.4)	10.6 (3.0)
Median	10.0	10.5	10.0
Min, Max	6.0, 16.0	6.0, 19.0	6.0, 19.0
MG-ADL total score at baseline Category, n (%)			
<=9	33 (38.4)	33 (37.5)	66 (37.9)
>=10	53 (61.6)	55 (62.5)	108 (62.1)
QMG total score at baseline			
Mean (SD)	18.7 (3.6)	19.4 (4.5)	19.1 (4.1)
Median	18.0	18.5	18.0
Min, Max	12, 31	13, 36	12, 36
Prior Thymectomy, n (%)	45 (52.3)	37 (42.0)	82 (47.1)
Prior MG Crisis, n (%)	28 (32.6)	29 (33.0)	57 (32.8)
gMG refractory*, n (%)	44 (51.2)	44 (50.0)	88 (50.6)

Source: modified from the Table 7-5 in the sponsor's study report, verified by the statistical reviewer.

*A subject 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 enrollment.

Abbreviations: gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = quantitative myasthenia gravis; SD = standard deviation

6.2.2.4.2. Efficacy Results of the Primary Endpoint

The results reported by the Applicant were confirmed by the statistical reviewer.

The primary analysis of MG-ADL included 174 subjects. There was a statistically significantly greater mean reduction in the change in MG-ADL total score from baseline to week 12 of the 12-week double-blind treatment phase for zilucoplan compared with placebo. The difference in least squares mean (LSM) (95% CI) was -2.09 (-3.24, -0.95) for zilucoplan 0.3 mg/kg versus placebo (p<0.001).

Table 13. Primary Endpoint Analyses of MG-ADL – mITT – Study MG0010

Characteristic	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
Baseline		
Mean (SD)	10.31 (2.51)	10.86 (3.40)
Median	10.0	10.5
Q1, Q3	8.0, 12.0	8.0, 13.0
Minimum, Maximum	6.0, 16.0	6.0, 19.0
Change from baseline in Week 12		
N	85	86
Mean (SD)	-4.49 (3.93)	-2.55 (3.83)
Median	-5.0	-2.0
Q1, Q3	-7.0, -1.0	-5.0, 0
Minimum, Maximum	-13.0, 4.0	-14.0, 6.0
Adjusted analysis		
LSM	-4.39	-2.30
(95% CI of LSM)	(-5.28, -3.50)	(-3.17, -1.43)
Difference in LSM		-2.09
(95% CI of difference)		(-3.24, -0.95)
p-value		<0.001

Source: reviewer's analysis and sponsor's analysis Table 8-1 and Table 14.2.1.6 in CSR verified by the reviewer.

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living, SD = Standard Deviation, LSM = Least Square Mean, CI = Confidence Interval.

The mixed model repeated measures (MMRM) model included treatment group (drug or placebo), region (North America, Europe, and East Asia), MG-ADL total score at baseline, QMG score at baseline, visit (week 1, 2, 4, 8 and 12), treatment by visit and baseline MG-ADL score by visit interactions. An unstructured covariance structure was used. P-values were for the comparison of treatment groups in change from baseline to week 12.

Any rescue therapy, MG crisis, or death were considered as treatment failure, and any related missing data were imputed using baseline or last value available, whichever was worse, i.e., WOCF.

A total of two subjects died during the double-blind period: one in the zilucoplan group and one in the placebo group.

Both subjects missed the week 12 (day 84) assessment for MG-ADL score since they both withdrew from the investigational medicinal product and died before the week 12 timepoint. One subject (b) (6) discontinued on day 17 and died on day 75; one subject (b) (6) discontinued on day 32 and died on day 43. Both subjects were included in the MMRM model with their day 84 MG-ADL score imputed using WOCF, i.e., the worst of baseline, or last value available, whichever was worse. For example, subject (b) (6) discontinued on day 17 and died on day 75; and, therefore, was missing the week 12 (day 84) assessment for MG-ADL score. This subject was included in the MMRM model with day 84 score set as 11.

The site inspection team noted some protocol deviations including the “acetylcholinesterase inhibitor therapy for less than 10 hours prior to evaluation.” An information request was sent, and the Applicant responded by sending an additional protocol deviation analysis dataset named

“DV10_May” in Study Number (SN) 38 with AVISIT and AVISITN populated allowing to identify the timepoints (baseline, day 8, day 15, day 29, day 57, day 84) in which the deviations occurred. The impact on primary efficacy result was small since these protocol deviations were rescue medication use and considered as treatment failure with a “WOCF” approach. The impact of deviations that happened at baseline before randomization, were minimal because of the randomization. There are 12 subjects (6 in each arm) in the protocol deviation analysis dataset with protocol deviation term (DVTERM) = “INCL6 not met, and subject has a QMG score of <12 at screening or baseline or are on acetylcholinesterase inhibitor therapy for less than 10 hours.” Even when excluding these 12 subjects from the primary analysis, the result is still significant (Diff -1.97, p =0.0012).

Additional Analysis After Refreshed Data Received in SN 38 With More Details About Protocol Deviations

There are two subjects, one from each arm: (b) (6) from placebo arm and (b) (6) from drug arm, who had received acetylcholinesterase inhibitor therapy <10 hours prior to day 84 assessments (Statistical Analysis System [SAS] dataset “dv10_may” submitted in SN 38, DVTERM= “Any change to dosing with cholinesterase inhibitor less than 10 hours prior to evaluation” and AVISIT= “day 84”). The result of the primary analysis remains significant even with the removal of these two subjects from primary efficacy analysis (mean diff -2.14 with p=0.0003).

There are 10 subjects, 5 from each arm, who had acetylcholinesterase inhibitor therapy <10 hours affecting post baseline (any of the 5 timepoints from day 8 to day 84) assessments. (SAS dataset “dv10_may” submitted in SN 38, DVTERM= “Any change to dosing with cholinesterase inhibitor less than 10 hours prior to evaluation” and AVISIT in (“day 8”, “day 15”, “day 29”, “day 57”, “day 84”). Two subjects in the placebo arm were flagged for more than one visit(s); one subject (b) (6) visited five times and one subject (b) (6) visited two times. In total 10 subjects with 15 lines of post baseline records were affected. By removing these from the main analysis, the result is still significant: mean diff -2.14 with p<0.001. Subject (b) (6) was from site 119 which was one of the sites selected for site inspection.

Table 14. Sensitivity Analyses After SN 38 for More Details on “ACh Inhibitor Therapy <10 h” Protocol Deviations

Prime Efficacy Analysis Result for Study MG0010	Estimate for Mean Diff	p-value
CSR Table 8 -1	-2.0939	0.0004
Remove Day 84 affected by DV in SN 38	-2.1463	0.0003
Remove any postbaseline from Day 8 to Day 84 affected by DV in SN38	-2.1359	0.0003

Source: Review’s analysis using Applicant’s data.
Abbreviations: DV = deviations; SN = study number

Given the similarity of the results across multiple sensitivity analyses, the results of the primary efficacy result reported by the Applicant have been confirmed.

6.2.2.4.3. Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and slightly higher in the placebo group. The strictly defined “missing” included those subjects who had MG-ADL scores but

NDA 216834

Zilucoplan

violated protocol requirement of not taking other medications within 10 hours of the assessment. More subjects in the placebo group had such protocol deviations. The “missing” after applying the clinical rule of “rescue meds/MG crisis/Death = treatment Failure” was very low, as can be seen in the following table that shows the missing data subject counts for each group.

Table 15. Subject Counts at Baseline and Week 1 to 12 – mITT – Study MG0010

Subject Counts	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 12 Missing	Missing %	Week 12 Still Missing After “Rescue/MG Crisis/Death = F” by WOCF	Missing % After WOCF
Zilucoplan	86	83	85	83	81	80	6	6.98%	1	1.16%
Placebo	88	87	84	78	78	75	13	14.77%	2	2.27%
Total	174	170	169	161	159	155	19	10.92%	3	1.72%

Source: Reviewer's own analysis.

Abbreviations: F = Treatment Failure; WOCF = Worst Observation Carry Forward.

In the sensitivity analyses performed by the Applicant, missing data were analyzed by imputing the placebo-based distribution with a J2R (jump-to-reference) approach. The primary endpoint was analyzed using the same MMRM model after the imputations. Per-protocol analysis was also performed. The results of the sensitivity analyses were consistent with those of the primary analysis.

Table 16. Sensitivity Analysis of MG-ADL for Missing Data – Study MG0010

Change from Baseline MG-ADL Total Score at Week 12	Placebo Based Imputation Using J2R Approach		Per-Protocol		CFS (COVID-19 Free Set)	
	Drug (N=86)	Placebo (N=88)	Drug (N=70)	Placebo (N=77)	Drug (N=77)	Placebo (N=81)
LSM	-4.47	-2.44	-4.48	-2.13	-4.42	-2.18
(95% CI)	(-5.35, -3.59)	(-3.31, -1.58)	(-5.42, -3.53)	(-3.02, -1.24)	(-5.30, -3.55)	(-3.03, -1.33)
Difference in LSM		-2.03		-2.35		-2.24
(95% CI)		(-3.16, -0.89)		(-3.56, -1.13)		(-3.37, -1.11)
p-value		<0.001		<0.001		<0.001

Source: Tables 8-2, 8-3 and 8-5 study report

Abbreviations: J2R = Jump to reference; CFS = COVID-19 Free Set; LSM = Least Square Mean; CI = Confidence Interval.

The COVID19-Free Set (CFS) was defined as mITT population who did not have COVID-19-related important protocol deviation, a visit reported as impacted by COVID-19, or a reported COVID-19 adverse event (AE). There were 158 out of 174 subjects (i.e., 90.8%) in the CFS.

As can be seen in the table above, the efficacy conclusion holds under sensitivity analyses using CFS by excluding the 16 subjects (9 in the drug arm and 7 in the placebo arm) who missed visits for COVID-19 related reasons such as decision to self-quarantine, diagnosis with COVID-19, and site/authority-imposed COVID-19 precautions.

6.2.2.4.4. Efficacy Results of the Secondary Endpoints

All three secondary endpoints in Family 1 and two out of four secondary endpoints in Family 2 were significant.

The three prespecified Family 1 secondary endpoints for this study were the following:

- Change from baseline to week 12 in QMG score
- Change from baseline to week 12 in MGC (Myasthenia Gravis Composite) score
- Change from baseline to week 12 in MG-QOL15r (Revised Myasthenia Gravis Quality of Life 15-item scale) Survey

Testing for Family 1 was done using a fixed-sequential testing procedure in the above prespecified order.

Change From Baseline in QMG Total Score at Week 12**Table 17. Secondary Endpoint: Change in QMG Score at Week 12– Study MG0010**

CFB QMG at Week 12	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
MMRM Model Adjusted Analyses		
LSM	-6.19	-3.25
Difference in LSM		-2.94
95% CI for the Difference in LSM		(-4.39, -1.49)
p-value		<0.001

Source: [Table 8-8 CSR](#).

Abbreviations: CI = confidence interval; LSM = least squares mean; MMRM = mixed model repeated measures; QMG = quantitative myasthenia gravis.

Change From Baseline in MGC Score at Week 12**Table 18. Secondary Endpoint: Change in MGC Score at Week 12– Study MG0010**

CFB MGC at Week 12	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
MMRM Model Adjusted Analyses		
LSM	-8.62	-5.42
Difference in LSM		-3.20
95% CI for the Difference in LSM		(-5.24, -1.16)
p-value		0.0023

Source: [Table 8-9 CSR](#).

Abbreviations: CI = confidence interval; LSM = least squares mean; MGC = myasthenia gravis composite.

Change From Baseline in MG-QOL15r Score at Week 12**Table 19. Secondary Endpoint: Change in MG-QOL15r Score at Week 12– Study MG0010**

CFB MG-QOL15r at Week 12	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
MMRM Model Adjusted Analyses		
LSM	-5.65	-3.16
Difference in LSM		-2.49
95% CI for the Difference in LSM		(-4.45, -0.54)
p-value		0.0128

Source: [Table 8-10 CSR](#).

Abbreviations: CI = confidence interval; LSM = least squares mean; MG-QOL15r = Revised Myasthenia Gravis Quality of Life 15-Item Scale; MMRM = mixed model repeated measures.

Since all endpoints in Family 1 were significant, Family 2 was tested. Two of the four secondary endpoints were significant in Family 2: MG-ADL responders (≥ 3 -point) and QMG responders (≥ 5 -point).

The four prespecified **Family 2** secondary endpoints for this study were:

- Proportion of subjects receiving rescue therapy over the 12-week treatment period
- Proportion of subjects with MG-ADL score of 0 or 1 at week 12 without rescue therapy
- Proportion of subjects with ≥ 3 points reduction in MG-ADL score at week 12 without rescue therapy
- Proportion of subjects with ≥ 5 points reduction in QMG score at week 12 without rescue therapy

Family 2 was tested using a multistep, step-down Holm procedure where the endpoints were tested in order of smallest p-value to largest p-value: comparing the smallest p to 0.0125, 0.017, 0.025, and 0.05. The nominal p-values for the four secondary endpoint in Family 2 were 0.1003, 0.0885, <0.001, and 0.0012. After the Holm procedure, the third and fourth endpoints in Family 2 were statistically significant. Missing data were imputed as nonresponder.

MG-ADL 3-Points Responders at Week 12

Table 20. Secondary Endpoint: MG-ADL 3-Points Responders at Week 12– MG0010

	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
MG-ADL 3-points responders at Week 12		
N	86	88
n	62	40
% Responders	72.09%	45.45%
Difference from Placebo		26.64%
Adjusted percentage	73.1%	46.1%
p-value		<.001

Source: modified from Table 8-11 and Table 14.2.6.5 study report, and reviewer's own analysis.

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living.

QMG 5-points Responders at Week 12

Table 21. Secondary Endpoint: QMG 5-Points Responders at Week 12– MG0010

	Zilucoplan 0.3 mg/kg (N=86)	Placebo (N=88)
QMG 5-points responders at Week 12		
N	86	88
n	49	28
% Responders	56.98%	31.82%
Difference from Placebo		25.16%
Adjusted percentage	58.0%	33.0%
p-value		.0012

Source: modified from Table 8-12 and Table 14.2.7.5 study report, and reviewer's own analysis.

Abbreviations: QMG = quantitative myasthenia gravis.

6.2.2.4.5. Findings in Subgroups – Age, Gender, and Race

Analyses for the treatment effect across subgroups such as age, gender, and race were performed. The trend in treatment success appears to be similar across subgroups.

Table 22. Age, Gender, and Race Summaries by Treatment Group – Study MG0010

	Age (≥65)	Gender (Female)	Race (White)	Race (Asian)	Race (Black)	Race (American Indian or Alaska Native)	Race (Missing)
Drug (n=88)	22	52	66	7	6	0	7
Placebo (n=86)	26	47	62	14	7	1	4
Overall (n=174)	48	99	128	21	13	1	11

Source: Table 7-4 and Table 8-14 in the sponsor's study report, verified by the statistical reviewer.

Note: Due to local regulations in France, race was not recorded.

Table 23. Findings in Subgroup Populations – Age, Gender, and Race – Study MG0010

MG-ADL Total Score	N	Baseline Mean (SD)	Change in Week 12(95% CI)	Diff (95% CI)
Age ≥65				
Drug	22	10.59 (2.86)	-4.41 (-6.08, -2.74)	-1.99 (-3.89, -0.09)
Placebo	26	10.23 (3.57)	-2.42 (-4.02, -0.82)	
Age <65				
Drug	64	10.22 (2.40)	-4.30 (-5.38, -3.21)	-2.22 (-3.67, -0.77)
Placebo	62	10.59 (2.86)	-2.07 (-3.16, -0.99)	
Gender=Female				
Drug	52	10.60 (2.32)	-4.13 (-5.38, -2.88)	-1.77 (-3.40, -0.15)
Placebo	47	11.09 (3.49)	-2.36 (-3.65, -1.06)	
Gender=Male				
Drug	34	9.88 (2.76)	-4.97 (-6.28, -3.66)	-2.81 (-4.49, -1.13)
Placebo	41	10.61 (3.32)	-2.16 (-3.36, -0.96)	
Race=White				
Drug	66	10.09 (2.48)	-4.42 (-5.30, -3.55)	-2.02 (-3.28, -0.76)
Placebo	62	10.98 (3.58)	-2.41 (-3.31, -1.50)	
Race=Black				
Drug	6	12.33 (2.07)	-7.34 (-12.79, -1.90)	-3.66 (-10.46, 3.14)
Placebo	7	9.71 (3.50)	-3.68 (-10.76, 3.39)	
Race=Asian				
Drug	7	10.71 (2.75)	-6.58 (-10.51, -2.65)	-3.00 (-7.02, 1.01)
Placebo	14	11.36 (2.95)	-3.58 (-6.02, -1.14)	
Race=All Other				
Drug	7	10.29 (2.63)	-2.66 (-8.14, 2.82)	-3.14 (-10.26, 3.98)
Placebo	5	9.60 (1.95)	0.48 (-5.27, 6.23)	

Source: Table 8-14 and Table 14.2.1.4 study report, and Reviewer's own analysis

Abbreviations: CI = confidence interval; MG-ADL = Myasthenia Gravis Activities of Daily Living; SD = standard deviation

The Applicant's subgroup analysis simply reported the observed descriptive summary such as mean and SD (standard deviation). Out of the total 6 versions of the study SAP, the original version did state that the same methodology of the primary efficacy analysis would be repeated for pre-defined subgroups, and that the result would be viewed as exploratory. The later five versions of SAP changed this part to reporting descriptive results with no statistical testing, citing their internal SAP template and team decision as the reason. The study report was created using the last version of the SAP. The original SAP regarding subgroup analysis reflects what has been used in recent drug reviews, i.e., applying the same methodology for primary efficacy analysis to pre-defined subgroups.

Therefore, the same MMRM model used in the primary endpoint analysis including the WOCF (worst observation carried forward) approach, was rerun on the subsets, and the estimates were reported descriptively without p-values, as can be seen in the above table.

6.2.2.4.6. Findings in Other Special Subgroups – Two Strata Variables: Region, Baseline MG-ADL Score Category

Baseline MG-ADL score category was defined as two levels: ≤ 9 and ≥ 10 . Baseline MG-ADL score and region, defined as North America, Europe, and East Asia, were used as two stratification factors.

Table 24. Region and Baseline MG-ADL Score Category Summaries by Treatment Group - Study MG0010

	Region North America	Region Europe	Region East Asia	Baseline MG- ADL Score ≤ 9	Baseline MG- ADL score ≥ 10
Drug (n=86)	45	34	7	33	53
Placebo (n=88)	46	33	9	35	53
Overall (n=174)	91	67	16	68	106

Source: Reviewer's own analysis

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living.

The trend in treatment success appears to be similar.

Table 25. Findings in Subgroup Populations -Region and Baseline MG-ADL Score Category-Study MG0010

MG-ADL total score	N	Baseline Mean (SD)	Change in Week 12(95% CI)	Diff (95% CI)
Baseline MG-ADL score ≤ 9				
Drug	33	7.70 (1.07)	-3.96 (-5.10, -2.82)	-1.89 (-3.35, -0.42)
Placebo	35	7.51 (0.98)	-2.07 (-3.18, -0.96)	
Baseline MG-ADL score ≥ 10				
Drug	53	11.94 (1.60)	-4.71 (-6.03, -3.40)	-2.32 (-4.05, -0.59)
Placebo	53	13.08 (2.49)	-2.39 (-3.69, -1.10)	
Region=North America				
Drug	45	10.42 (2.60)	-4.55 (-5.67, -3.43)	-1.30 (-2.88, 0.29)
Placebo	46	11.13 (3.66)	-3.25 (-4.37, -2.14)	

Region=Europe				
Drug	34	10.09 (2.40)	-4.49 (-5.83, -3.15)	-2.59 (-4.50, -0.67)
Placebo	33	10.45 (3.07)	-1.90 (-3.27, -0.54)	
Region=East Asia				
Drug	7	10.71 (2.75)	-4.68 (-7.41, -1.95)	-4.21 (-7.89, -0.53)
Placebo	9	11.00 (3.39)	-0.47 (-2.87, 1.92)	

Source: Table 8-14 and Table 14.2.1.4 study report, and Reviewer's own analysis

Abbreviations: CI = confidence interval; MD-ADL = Myasthenia Gravis Activities of Daily Living

The exact same MMRM model used in the primary endpoint analysis including the WOCF approach, was rerun on the subsets, and the estimates were reported descriptively without p-values, as can be seen in the above table.

Statistical Issues and Conclusions

No major statistical issues were identified. There was only one single Phase 3 study to review, and it provided statistical evidence that zilucoplan 0.3 mg/kg is effective in treating patients with gMG.

The efficacy results obtained from the statistical analyses of the one pivotal study support the conclusion that zilucoplan 0.3 mg/kg is effective in treating patients with gMG.

Most enrolled subjects completed the study. All completers entered the extension. These factors were balanced.

Subjects were balanced demographically except for sex, which does not appear to have biased the efficacy results.

Subjects resembled the wider MG population (mean age 53 years, 28% >65 years, mean BMI 31 kg/m², 74% white) and were balanced in these factors between groups. The two groups were geographically balanced (52% were North American, 39% were European, and 9% were Asian.).

Baseline myasthenia characteristics were balanced between groups as reflected in disease duration, disease severity, mean age at disease onset of 44 years, mean disease duration 9 years, median MG-ADL 10, median QMG 18, 100% on concomitant medications used to treat MG (97% on cholinesterase inhibitors, 87% on steroids, 69% on immunoglobulin or plasma exchange), which were balanced between groups.

Table 26. Baseline Demographics and Clinical Characteristics, Safety Population, Study MG0010

Characteristic	Zilucoplan N=86	Placebo N=88
Sex, n (%)		
Female	52 (60.5)	47 (53.4)
Male	34 (39.5)	41 (46.6)
Age, years		
Mean (SD)	52.6 (14.6)	53.3 (15.7)
Median (min, max)	54.5 (21, 75)	55.5 (19, 75)
Age group, years, n (%)		
18 to <65 years	64 (74.4)	62 (70.5)
65 to <75 years	21 (24.4)	23 (26.1)
75 to <85 years	1 (1.2)	3 (3.4)

Characteristic	Zilucoplan N=86	Placebo N=88
Age group ≥65, years, n (%)		
≥65	22 (25.6)	26 (29.5)
Age group ≥75, years, n (%)		
≥75	1 (1.2)	3 (3.4)
Race, n (%)		
American Indian or Alaska Native	0	1 (1.1)
Asian	7 (8.1)	14 (15.9)
Black or African American	6 (7.0)	7 (8.0)
Not Reported	2 (2.3)	1 (1.1)
Unknown	1 (1.2)	0
White	66 (76.7)	62 (70.5)
Missing	4 (4.7)	3 (3.4)
Ethnicity, n (%)		
Hispanic or Latino	7 (8.1)	5 (5.7)
Not Hispanic or Latino	72 (83.7)	79 (89.8)
Not Reported	1 (1.2)	1 (1.1)
Unknown	2 (2.3)	0
Missing	4 (4.7)	3 (3.4)
Country of participation, n (%)		
Great Britain	12 (14.0)	7 (8.0)
Japan	7 (8.1)	9 (10.2)
Poland	11 (12.8)	12 (13.6)
United States	45 (52.3)	43 (48.9)
Others	11 (12.8)	17 (19.3)
Region of participation, n (%)		
East Asia	7 (8.1)	9 (10.2)
Europe	34 (39.5)	33 (37.5)
North America	45 (52.3)	46 (52.3)
Is in United States, n (%)		
United States	45 (52.3)	43 (48.9)
Non-United States	41 (47.7)	45 (51.1)

Source: FDA-generated table
Abbreviations: SD = standard deviation

6.3. Key Efficacy Review Issues

Not applicable.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Widespread inflammatory effects and liver and pancreas histopathology, with correlating clinical pathology changes, were consistent findings in the 4-, 13-, and 39-week toxicity studies conducted in cynomolgus monkey.

In a 4-week study in the monkey (0, 1, 2, or 4 mg/kg/day), drug-related effects included elevated bile acids and lipase and peribiliary mixed cell inflammation in the liver at the MD and HD.

In the 13-week study (0, 0.25, 1, 2, or 10 mg/kg/day), hepatic and pancreatic enzymes were increased in individual animals at all doses and bile acids were increased at the HD. Histopathologic changes in the pancreas included marked inflammation (vasculitis), acinar degeneration, and ductular hyperplasia with correlative increases in amylase and lipase in one HD male and less severe pancreatic acinar degeneration in single females from each of the ≥ 1 mg/kg/day dose groups. Following a 4-week recovery period, acinar atrophy and ductular hyperplasia with mononuclear infiltrates in the pancreas and bridging bile duct and oval cell hyperplasia with fibrosis in the liver were found in one of the two HD males examined. Multi-organ mononuclear infiltrates in the pancreas, kidney, tongue, esophagus, salivary gland, thyroid, rectum, stomach, and urinary bladder were observed at all doses in males and females. The pancreas findings at the HD were considered dose-limiting.

In the 39-week study (0, 0.25, 1, 2, 4, or 6 mg/kg/day), all doses were associated with inflammatory cell infiltrates of most organs. In 3 animals that were sacrificed early due to moribund condition (LD animal on Day 245 with colitis, MHD (4 mg/kg) and HD animals on days 52 and 203, respectively, with skin ulcerations and erosions) histopathology findings included liver fibrosis (HD) and pancreatic acinar degeneration (all 3 animals) or pancreatic duct degeneration/regeneration with acinar atrophy (LD), with associated increases in amylase and lipase at the 2 highest doses. Pancreatic acinar cell degeneration with fibrosis/fibroplasia was also found in 1 MD (2 mg/kg) animal at the scheduled terminal sacrifice. A NOAEL was not established; at what was considered the highest tolerated dose (2 mg/kg/day), exposure was approximately 2X the maximal predicted clinical exposure.

Table 27. Estimated Safety Margins.

Study	NOAEL or highest tolerated dose (mg/kg/day)	Observed exposure at NOAEL or highest tolerated dose		Safety margin modelling approach ^a		Safety margin based on ethnic bridging study ^b	
		C _{max} (µg/mL)	AUC (µg.h/mL)	C _{max}	AUC	C _{max}	AUC
13-week cyno	2	34.05	573.5	1.6	2.1	2.7	2.2
39-week cyno ^c	2 ^c	32.25	541	1.6	2.0	2.6	2.1

Source: Table 4–2 (Page 34) in 2.4 Nonclinical Overview

a Safety margins based on predicted exposure of an 80kg patient receiving a 32.4mg dose with a C_{max} of 20.7µg/mL and an AUC of 275µg.h/mL (CL0529).

b Data from the clinical ethnic bridging study (UP0113 in Table 14.2.2.4 arithmetic mean of Caucasian group on Day 14) total C_{max} and AUC of zilucoplan were 12.4µg/mL and 256µg.h/mL

c Safety margins based on highest tolerated dose.

Adverse reproductive and developmental effects of zilucoplan (0, 1, 2, or 4 mg/kg/day) were observed in a male fertility study and an enhanced pre- and postnatal (with embryofetal component) development study in monkey (reference Pregnancy and Lactation section).

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The main safety concern with inhibitors of complement C5 activity is infection with encapsulated organisms such as *Neisseria* species (e.g., particularly *N. meningitidis* for C5 targeting therapy) and, in children, *Streptococcus pneumoniae* and *Hemophilus influenza* Type

B. Immunosuppressed patients may also be at risk for atypical bacterial or fungal infections (e.g., aspergillosis).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable.

7.3.1. Adverse Events Identified in Postmarket Experiences

Not applicable. Zilucoplan is a new molecular entity.

7.3.2. Expectations on Safety

Because zilucoplan is a complement C5 inhibitor, there is a risk for meningococcal infection for which a Risk Evaluation and Mitigation Strategy (REMS) will be imposed. Warnings and Precautions in labeling will address meningococcal infections and other serious infections.

Pancreatitis and other serious pancreatic adverse events have been identified in these studies and will also be described in Warnings and Precautions.

Pharmacovigilance at FDA will conduct ongoing safety evaluations of post-market reports of serious infections and pancreatic adverse events.

The safety of zilucoplan in women who are pregnant or breastfeeding, and in infants who are breastfeeding, has not been characterized in these clinical trials. Because zilucoplan will be used in women of childbearing potential, a pregnancy outcomes study and a lactation pharmacokinetic study will be requested post-marketing requirements (see Section [24](#)).

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

Data from placebo-controlled phase and extensions of studies MG0010, MG0009, and MG0011 form the basis for clinical safety evaluation in this review. Pivotal Study MG0010 enrolled 174 subjects. The dose-finding phase 2 study MG0009 (44 subjects randomized to 3 dose levels), which had both a placebo-controlled portion and its own extension, plays a supportive role. The placebo-controlled studies (MG0009 DB and MG0010) and long-term extensions (MG0009 OLE and MG0011) in MG were analyzed separately. The long-term safety data was utilized for the analysis of pancreatic events, which took longer to manifest than the 12-week duration of the placebo-controlled studies.

The Applicant's mapping of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) is acceptable. Safety analyses were based on preferred terms (PT). However, in the case of verifying the Applicant's proposed AE table for the prescribing information, pooling of PT terms resulted in slightly different adverse event counts. Treatment-emergent (TE) was not defined in the protocols—see applicable discussions of treatment-emergent adverse events. These studies used the National Cancer Institute Common Terminology Criteria for Adverse Events criteria for assessing adverse event severity. The definitions of SAEs were compliant with 21 CFR.

Because of issues with the quality of the AE and lab records data in studies MG0009 and MG0010, the safety datasets for studies MG0009, MG0010, and MG0011 were analyzed separately. The Applicant's pooled analyses were not utilized in this review, as the pooling scheme was inadequate (b) (4)

7.5. Adequacy of the Clinical Safety Database

In the original submission (excluding the 120-day update data), the Applicant reported 213 subjects with gMG were exposed to the to-be-marketed investigational medicinal product dose of 0.3 mg/kg, 87 of whom received the 0.3 mg/kg dose for at least 1 year.

There were approximately 260 patient-years of exposure to any zilucoplan dose and approximately 254 patient-years of exposure to zilucoplan 0.3 mg/kg (to-be-marketed dose) excluding the 120-day update. At the 120-day update there were 329 patient-years of exposure to zilucoplan 0.3 mg/kg – 191 subjects for at least 6 months and 131 subjects for at least 1 year [ref: Table 1-4 in Applicant's 0001 submission, Summary of Clinical Safety 120-day safety update]. The Applicant's exposure numbers could not be exactly replicated (despite multiple IRs), although the estimates were within a few patient-years of the Applicant's calculation.

7.6. Safety Results

7.6.1. Safety Results

7.6.1.1. Overview of Treatment-Emergent Adverse Events

Adverse event (AE) refers to non-SAEs or SAEs in these sections, depending on context, unless otherwise noted.

[Table 28](#) is a summary of treatment-emergent (TE) adverse events in Study MG0010. There were slightly more AEs leading to study drug discontinuation or interruption in the zilucoplan group compared to placebo. There was one death each in the zilucoplan and placebo groups.

Table 28. Overview of Adverse Events, Safety Population, Trial mg0010

Event Category	Zilucoplan N=86 n (%)	Placebo N=88 n (%)	Zilucoplan vs. Placebo Risk Difference (%) (95% CI)
SAE	11 (12.8)	13 (14.8)	-2.0 (-12.2, 8.3)
SAEs with fatal outcome	1 (1.2)	1 (1.1)	0.1 (-) **
Life-threatening SAEs	1 (1.2)	0	1.2 (-) **
AE leading to permanent discontinuation of study drug	4 (4.7)	(1.1)	3.6 (-) **
AE leading to dose modification of study drug	5 (5.8)	4 (4.5)	1.3 (-) **
AE leading to interruption of study drug	5 (5.8)	4 (4.5)	1.3 (-) **
AE leading to reduction of study drug	0	0	0 (-) **
AE leading to dose delay of study drug	0	0	0 (-) **
Other	0	0	0 (-) **
Any AE	66 (76.7)	62 (70.5)	6.3 (-6.8, 19.4)
Severe and worse	10 (11.6)	10 (11.4)	0.3 (-9.2, 9.7)
Moderate	20 (23.3)	23 (26.1)	-2.9 (-15.7, 9.9)
Mild	36 (41.9)	29 (33.0)	8.9 (-5.4, 23.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that had a start date on or following the first dose of study treatment (active or placebo) or an AE that increases in severity after treatment start if the event was present at the time of treatment start.

Duration is 12 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

** Counts are too small to provide a meaningful estimate of the 95% CI.

Severity as assessed by the investigator.

The Clinical Study Report indicates two adverse events leading to permanent study discontinuation in the placebo group. The CDS STF report includes only 1 because the adverse event leading to death (Cerebral hemorrhage) of subject (b) (6) is not coded as leading to study discontinuation. This subject is added to the discontinuations in the placebo group.

The Clinical Study Report indicates 11 subjects who experienced a severe AE and 22 who experienced a moderate AE in the placebo group. The CDS STF report includes 10 and 23, respectively, because there is one AE (Cerebrovascular accident) of subject (b) (6) that is attributed to trial mg0011 in the ISS dataset instead of trial mg0010.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Treatment-Emergent (TE) Deaths

There were 10 TE deaths in studies MG0009, MG0010, and MG0011 as of data lock for this submission (excluding the 120-day update). This analysis applies only to the data as of the lock date of the original submission and not to the 120-day update, unless otherwise noted.

In study MG0010, there were two TE deaths, one in each treatment group:

- One death in zilucoplan group (subject (b) (6))—COVID-19 pneumonia on day 18 of zilucoplan in a 42 years-of-age subject with asthma, obesity, type 2 diabetes mellitus, hypothyroidism, and sleep apnea
- One death in placebo group (subject (b) (6))—cerebral hemorrhage on day 32 in a 57 years-of-age subject with hypertension and type 1 diabetes mellitus

In the double-blind period of study MG0009, there were no TE deaths.

In study MG0009 OLE period, there were three TE deaths (7%), all in subjects on zilucoplan 0.3 mg/kg:

- Subject MG0009-(b) (6): COVID-19 infection at 644 days. Multiple high-risk comorbidities included chronic obstructive pulmonary disease, chronic prednisone, coronary stents, peripheral vascular disease, and others.
- Subject MG0009-(b) (6): Respiratory failure and cardiac arrest 188 days after start of zilucoplan, attributed to poorly controlled diabetes mellitus and “prominent vascularity” (autopsy result).
- Subject MG0009-(b) (6): Advanced metastatic (Stage 4) pancreatic adenocarcinoma first identified 241 days after start of zilucoplan 0.3 mg/kg. Medical history was significant for acute pancreatitis, metabolic syndrome, coronary artery disease, hyperlipidemia, sleep apnea, and others. Also see section below on pancreatic AEs.

In study MG0011, there were five TE deaths, all of which occurred on zilucoplan 0.3 mg/kg:

- Subject MG0010-MG0011/(b) (6): The Applicant did not classify this death as treatment-emergent (see Section III.22 for data integrity issues). Consequently, it was excluded from some of the AE datasets and analyses the Applicant submitted. However, this death was clearly TE, as it was a fatal outcome of an AE of pancreatic mass (pancreatic adenocarcinoma) diagnosed months before the sequence of events leading to death and discontinuation from study MG0011. This death was at the subject’s home (b) (6) in hospice care seven weeks after the last zilucoplan dose (b) (6)
- Subject MG0010-MG0011/(b) (6): Unwitnessed, fatal, blunt head trauma 126 days after first zilucoplan injection in study MG0010 (45 days into study MG0011). Autopsy was performed, and no results were submitted by the Applicant.
- Subject MG0010-MG0011/(b) (6): Cardiac arrest after 120 days of zilucoplan (including study MG0010) in a subject with a history of past myocardial infarction (MI), hyperlipidemia, hypertension, and other comorbidities.
- Subject MG0011-(b) (6): Death of unknown cause 88 days after first zilucoplan injection in study MG0011. However, this death was likely from metastatic prostate cancer based on the

past medical history of prostate cancer, and elevated prostate-specific antigen as well as metastatic lesions found on the flat bones (pelvis and scapula) on positron emission tomography (PET) scan before death. Past medical history included prostate enlargement (transurethral resection of the prostate (TURP), possibly cancer), (CHF), type 2 insulin-dependent diabetes mellitus, hyperlipidemia, hypertension, and hepatitis, among other conditions.

- Subject MG0009-MG0011/ (b) (6): Cardiac arrest of unknown etiology 1,283 days after first zilucoplan injection in study MG0009. Medical history included aortic dissection, hypertension, thymectomy, insomnia, and anxiety.

In Study MG0010, seven subjects developed COVID-19 infection – three subjects on zilucoplan and four subjects on placebo. In Study MG0010, there was one death from COVID, and this occurred in the zilucoplan group. In study MG0011, six subjects had an SAE of COVID-19 that resolved.

There were two deaths in these trials from advanced pancreatic adenocarcinoma, where zilucoplan was continued through antecedent pancreatic events and medical evaluations.

7.6.1.3. Treatment-Emergent Serious Adverse Events (TESAEs)

In this section and throughout this review, the notation SAE refers to treatment-emergent serious adverse events (TESAEs). Because of recurring issues of irreconcilable AE record counts with each information request, the counts below may differ from the Applicant's for the individual studies.

There were no designated medical events in any of these studies, except for acute pancreatitis, which is discussed at length in other safety sections of this review.

[Table 29](#) shows the SAE counts in Study MG0010 (referred to as Study 1 in the USPI) and shows that the SAEs were distributed as very small counts among different categories. The proportion of subjects with an SAE was not significantly different for zilucoplan (13%) than placebo (15%).

Table 29. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial MG0010

System Organ Class Preferred Term	Zilucoplan N=86 n (%)	Placebo N=88 n (%)
Any SAE	11 (12.8)	13 (14.8)
Blood and lymphatic system disorders (SOC)	1 (1.2)	0
Anemia	1 (1.2)	0
Gastrointestinal disorders (SOC)	1 (1.2)	1 (1.1)
Aphthous ulcer	1 (1.2)	0
Vomiting	0	1 (1.1)
Infections and infestations (SOC)	4 (4.7)	4 (4.5)
Esophageal candidiasis	1 (1.2)	0
Oral candidiasis	1 (1.2)	0
Pneumonia	1 (1.2)	0
Sepsis	1 (1.2)	0

System Organ Class Preferred Term	Zilucoplan N=86 n (%)	Placebo N=88 n (%)
COVID-19	1 (1.2)	2 (2.3)
COVID-19 pneumonia	1 (1.2)	2 (2.3)
Herpes simplex meningoencephalitis	0	1 (1.1)
Investigations (SOC)	1 (1.2)	0
Lipase increased	1 (1.2)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	1 (1.2)	0
Basal cell carcinoma	1 (1.2)	0
Nervous system disorders (SOC)	2 (2.3)	6 (6.8)
Cerebral hemorrhage	0	1 (1.1)
Myasthenia gravis	2 (2.3)	5 (5.7)
Pregnancy, puerperium, and perinatal conditions (SOC)	0	1 (1.1)
Hyperemesis gravidarum	0	1 (1.1)
Respiratory, thoracic, and mediastinal disorders (SOC)	1 (1.2)	1 (1.1)
Pulmonary embolism	1 (1.2)	0
Chronic obstructive pulmonary disease	0	1 (1.1)
Skin and subcutaneous tissue disorders (SOC)	1 (1.2)	0
Angioedema	1 (1.2)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that had a start date on or following the first dose of study treatment (active or placebo) or an AE that increases in severity after treatment start if the event was present at the time of treatment start.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 12 weeks.

Abbreviations: N = number of subjects in treatment arm; n = number of subjects with adverse event; SAE = serious adverse event; SOC = system organ class

In the double-blind period of Study MG0009, there were nine SAEs in eight subjects, approximately evenly divided among the three treatment groups: 3/15 subjects in the placebo group, 0/15 subjects in the 0.1 mg/kg zilucoplan group, and 5/14 subjects in the 0.3 mg/kg zilucoplan group (3 infections, 1 inflammation, 1 musculoskeletal chest pain).

In study MG0009 OLE portion, there were 44 SAEs: 27 SAEs on 0.3 mg/kg compared to 17 SAEs on 0.1 mg/kg. According to the original MG0009 protocol (version 3), the blind was maintained during the OLE, and subjects receiving placebo were randomized 1:1 to 0.1 mg/kg or 0.3 mg/kg. However, at some point during the ongoing studies, the protocol was amended, and switch all patients in the open-label studies to a dose level of 0.3 mg/kg zilucoplan.

In study MG0009 OLE, the following SAEs were reported:

- Five pancreatic SAEs in three subjects (all on 0.3 mg/kg) – one acute pancreatitis, one pancreatic carcinoma, one pancreatic cyst, and two infected pancreatic pseudocysts.
- Four SAEs of myasthenia gravis¹ in four subjects (one subject on 0.1 mg/kg, and three subjects on 0.3 mg/kg)

¹ Myasthenia gravis as an adverse event was not defined in these protocols and was based on the clinical judgment of the investigator.

- 11 infection SAEs in 8 subjects (four subjects on 0.1 mg/kg, and three subjects on 0.3 mg/kg, and one subject on placebo) – 1 COVID, 4 pneumonia, 2 staph bacteremia, 1 sepsis, 1 gastrointestinal infection, 1 liver abscess, 1 HSV2 encephalitis (placebo).
- Seven cardiac SAEs in four subjects (one subject on 0.1 mg/kg and three subjects on 0.3 mg/kg) – one fatal cardiac arrest, one bradycardia, one postoperative hypertension, as well as one MI and three atrial fibrillation/flutter SAEs in the same subject
- Remaining SAEs: Three renal calculus cases, two cholecystitis, two abdominal pain, two postprocedural complications, one back pain, one spinal fracture, one gastric ulcer, one respiratory failure, one noncardiac chest pain, one elevated fibrin D-dimer, and one syncope

In study MG0011, there were 118 SAEs in 46 subjects, as follows:

- Infection: 25 SAEs in 12 subjects. Among the 25 SAEs were multiple records of similar or the same SAEs on the same day that were related to each other. Accounting for these, there were 18 unique SAEs, and some subjects experienced multiple of these.

These SAEs were distributed as follows—six COVID (six subjects, all with pneumonia), one candida endocarditis (one subject)², four sepsis (three subjects), three non-COVID-associated pneumonia (three subjects—note that one klebsiella pneumonia urinary tract infection (UTI) was MedDRA-coded incorrectly as “Pneumonia”), two non-COVID-associated sepsis (two subjects), one hepatitis C (one subject), one liver abscess (one subject), one gastrointestinal viral infection (one subject), one staph infection of left shoulder (one subject), and one postprocedural sepsis following endoscopic retrograde cholangiopancreatography (ERCP) (one subject).

- MG exacerbation (Bhatia et al. 2001): 20 episodes of MG exacerbations (1 crisis where zilucoplan was withdrawn) in 12 subjects—14 severe and 7 moderate in severity
- Cardiac: 16 SAEs in 10 subjects, some with more than one cardiac SAE: 2 cardiac arrest (two subjects) both fatal, 3 nonfatal MI (three subjects), 4 Atrial fib/flutter (two subjects), 1 cardiac failure (one subject), 1 angina (one subject), 1 coronary thrombosis (in one subject with an MI 9 months earlier), 1 coronary artery disease (one subject), 1 bradycardia (one subject), and 1 pulseless electrical activity (one subject), 1 irregular heartrate (one subject)
- Pancreatic: Six episodes (four subjects), all severe. See Section 7.7.1 for further discussion.
- Biliary: Four SAEs in three subjects. Cholecystitis (two), cholangitis (one), bile duct stenosis (one)
- Stroke: Two strokes (two subjects)—one embolic (immediately post ablation for atrial fibrillation) and one ischemic

² Subject (b) (6) developed endocarditis and multiple other SAE infections preceding it (acinetobacter, brevibacterium, and corynebacterium) and following it (staph bacteremia, systemic inflammatory response syndrome) it. This subject had a very complex medical history including diabetes mellitus among other conditions as well as long-term corticosteroid use at the time of fungal endocarditis. This subject had also been on prophylactic amoxicillin and atovaquone (for pneumocystis carinii) for 5 years prior to zilucoplan.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation

Treatment discontinuation is not a meaningful measure of the clinical significance of an AE or SAE in these studies. There were no dose modification/discontinuation criteria in the protocols, and therefore, dose modification was at the discretion of the investigator (or sponsor). Few investigators attributed pancreatic SAEs as related to zilucoplan. Therefore, zilucoplan was usually continued through acute pancreatic conditions, including SAEs.

Nonetheless, based on terms used in the ADAE datasets, the following list shows the distribution of “withdrawals” and “interruptions”, terms not further defined:

- Study MG0009: 22 in 14 subjects. Some subjects had both SAEs and non-SAEs.
 - Withdrawals: Six subjects (one on placebo, five on zilucoplan 0.3 mg/kg)
 - Two deaths, both in OL portion: one pancreatic cancer death and one COVID death
 - One subject receiving placebo in the double-blind period for MG exacerbation (SAE)
 - Three in OL portion: one SAE of Grade 3 pneumonia related to zilucoplan, one AE of moderate dizziness, and one AE of mild musculoskeletal pain
 - Interruptions: 16 in 8 subjects (1 on placebo, 1 on zilucoplan 0.1 mg/kg, and 6 on zilucoplan 0.3 mg/kg)
 - SAEs—myocardial infarction, noncardiac chest pain, syncope; sepsis; nephrolithiasis, abdominal pain (on placebo), diverticulitis, systemic inflammatory response syndrome.
 - Non-SAEs—Two high lipase; dehydration, hypokalemia (on placebo); viral infection, abdominal abscess, rectal fistula (on placebo); atrial fibrillation
- Study MG0010: 23 in 13 subjects. Some subjects had both SAEs and non-SAEs.
 - Withdrawals: Five subjects (one SAE of hyperemesis gravidarum on placebo; four on zilucoplan 0.3 mg/kg—SAEs of aphthous ulcer and COVID-19, AEs of mouth ulceration and hepatic enzyme increase). The hepatic enzyme increase occurred after 2 weeks of zilucoplan (GGT >10X upper limit of normal [ULN]) and is discussed in a later section
 - Interruptions: 18 in 9 subjects (some subjects had both SAEs and non-SAEs)
 - SAEs: Four subjects on placebo (COPD, herpes simplex meningoencephalitis, myasthenia gravis, and vomiting); four subjects on zilucoplan 0.3 mg/kg (myasthenia gravis and pneumonia, high lipase, angioedema, and sepsis)
 - Non-SAEs: Nine events in four subjects (all on zilucoplan 0.3 mg/kg): epigastric pain, tonsillitis, sepsis, urticaria, abdominal pain, and vomiting.

- Study MG0011: 50 in 24 subjects (all on zilucoplan 0.3 mg/kg). Some subjects had both SAEs and non-SAEs.
 - Withdrawals: 12 subjects with 18 reasons for withdrawal reported
 - SAEs: Seven subjects with one or more SAEs at the time of withdrawal: two cardiac arrest, one sepsis/CAD/MG crisis, one MG crisis/aspiration pneumonia, one myasthenia gravis, one ischemic stroke, and one musculoskeletal pain
 - Non-SAEs: Seven events in six subjects. Three subjects with MG exacerbation, one subject with high lipase, one injection site burning/flatulence, and one kidney dysfunction
 - Interruptions: 32 AEs in 14 subjects
 - SAEs: 21 in 9 subjects (one subject (b) (6) had 10 SAEs, some of which occurred at the same visit, including a subject with pancreatic cyst incidentally identified in a nephrolithiasis hospitalization). SAEs included MI, COVID-19, one acute kidney injury, non-cardiac chest pain, syncope, respiratory failure, and amnesia.
 - Non-SAEs: 11 in 9 subjects: lipase increased, amylase increased, hypokalemia, MG exacerbation, COVID-19, atrial fibrillation, viral pneumonia (respiratory syncytial virus, COVID-19), bursitis, anal fistula, and abdominal neoplasm

The reasons for zilucoplan discontinuation were varied.

7.6.1.5. Treatment-Emergent Adverse Events

This section is a review of TEAEs, including SAEs. Here ‘AE’ denotes treatment-emergent adverse events generally and includes treatment-emergent SAEs, unless otherwise noted.

The analysis of the TEAEs and counts (b) (4)
 (b) (4) For study MG0010, [Table 30](#) shows the reviewer analysis of TE adverse events in at least 5% of subjects on zilucoplan and greater than placebo. (b) (4)

Table 30. Treatment-Emergent Adverse Events Occurring at Least 5% of Subjects Treated With Zilucoplan and More Frequently Than Placebo, Phase 3 Study MG0010

Body System Adverse Reaction	Zilucoplan 0.3 mg/kg (n=86) n (%)	Placebo (n=88) n (%)
General disorders and administration site conditions		
Injection site reactions ^a	25 (29.0)	14 (15.9)
Infections and Infestations		
Upper respiratory tract infections ^b	12 (14.0)	6 (6.8)

Body System Adverse Reaction	Zilucoplan 0.3 mg/kg (n=86) n (%)	Placebo (n=88) n (%)
Urinary tract infection	7 (8.1)	4 (4.6)
Gastro-intestinal disorders		
Diarrhea	9 (10.5)	2 (2.3)
Nausea or Vomiting ^c	7 (8.1)	6 (6.8)
Nervous system disorders		
Myasthenia gravis	9 (10.5)	8 (9.1)
Investigations		
Lipase increased	6 (7.0)	0 (0.0)
Amylase increased	5 (5.8)	1 (1.1)

Source: Reviewer-generated table.

^a Includes injection site bruising, injection site hematoma, injection site pain, injection site reaction, injection site hemorrhage, injection site rash, and abdominal or extremity contusion considered related to zilucoplan by investigator (b) (4)

^b Includes nasopharyngitis, upper respiratory tract infection, sinusitis, and tonsillitis

^c Includes the Preferred Term Nausea and/or the Preferred Term Vomiting

There was a discrepancy in AE counts between the reviewer's analysis and the Applicant's analysis in the high-lipase AE counts. The initial count was 7 in the zilucoplan arm and 1 in the placebo arm. However, subsequent inspection of the data in ADAE (study MG0010) revealed that two of the high-lipase AEs (one in each arm) were not actually treatment emergent, as they were listed as having onset on the same exact day therapy was initiated in MG0010, and therefore would give a misleading impression of having been associated with the therapy in MG0010. The same issue occurred with the high-amylase AEs, where a high-amylase AE in the placebo arm occurred on the same day of treatment initiation in MG0010.

In the double-blind period of Study MG0009, there were 169 AEs in 41 (93%) subjects, evenly divided among the 3 treatment arms. The most common AE was headache with 15 episodes (13 subjects) evenly divided among the 3 arms; 4 of these AEs were 'migraine with aura' in one subject over 4 days and were in the 0.3 mg/kg arm. The next most common AEs were each divided evenly among arms—11 injection site reactions (9 subjects, more common in zilucoplan group), 5 MG exacerbations (five subjects), and five AEs of dizziness (five subjects).

The higher rate of the AE of lipase increased in the zilucoplan group than the placebo group is consistent with the nonclinical pancreatic findings.

In study MG0009 OLE portion, there were 447 AEs in 42 subjects, which were balanced between the 0.1 mg/kg group (225 AEs in 22 subjects) and the 0.3 mg/kg group (222 AEs in 20 subjects). The most common AEs representing the most subjects were balanced between groups, and included upper respiratory tract symptoms, cough, gastrointestinal (GI) symptoms, injection site reactions, and myalgia/arthralgia.

In Study MG0011, there were 1,374 AEs in 164 subjects. The most frequent AE was headache (33 subjects), followed by MG exacerbation (28), COVID-19 (25), nonspecific viral symptoms. Injection site reactions, and dizziness, among others.

See Section 7.7.1 for further discussion of treatment emergent adverse events related to pancreatitis and other pancreatic conditions.

7.6.1.6. Laboratory Findings

This section focuses on lipase levels, which were a frequently scheduled laboratory assessment in these protocols. Serum lipase elevation is the result of pancreatic acinar cell injury and is a sensitive and specific indicator of exocrine pancreatic acinar cell injury.

Serum Lipase Levels in the Laboratory Data

In these studies, serum lipase (and amylase) elevations were mostly not captured as AEs but rather as scheduled laboratory data throughout these studies. Conversely, lipase elevations that occurred in most pancreatic AEs were not captured in these laboratory data. Therefore, the data reviewed here, which are based on the ADLB dataset, are for scheduled lipase levels unless otherwise noted. In ADLB there were relatively few unscheduled serum lipase levels.

An extensive analysis of the serum lipase data can be seen in Section [17.2](#) of this review.

In the placebo-controlled studies, mean serum lipase level increased by 40-44 U/L by day 57 in the zilucoplan 0.3 mg/kg group compared to placebo (2 U/L increase), and remained elevated by 20 U/L over baseline at day 84 (end of study in MG0010). This same trend also occurred in subjects newly initiating zilucoplan after being on placebo in antecedent studies MG0009 or MG0010.

In Study MG0010, six (7%) subjects on zilucoplan had an increase from a normal baseline lipase to a level >3x ULN by day 57 or 84, as compared to 0 (0%) on placebo (p=0.0133, 2-sided exact trend test). Lipase (or amylase) >3x ULN is one of the three American College of Gastroenterology criteria³ for acute pancreatitis (Tenner et al. 2013) (the other two criteria are typical abdominal pain and characteristic findings on abdominal imaging).

There were only a few cases of isolated amylase elevation, and most lipase elevations occurred in conjunction with amylase elevations. See Section [17](#). The amylase analysis does not change my conclusions about lipase.

7.6.1.7. Assessment of Drug-Induced Liver Injury, All Studies

There were no serious drug-related hepatic disorders.

In Study MG0010, there were two subjects with liver enzymes greater than 10X ULN, which involved only GGT:

- Subject (b) (6) in the placebo group in Japan with GGT=650 U/L (ULN=61 U/L) on day 84 (final visit) of MG0010. This subject was rolled into MG0011. At a rescue therapy visit 9 months (Day 267) into MG0011, GGT=703 U/L (ULN=61 U/L). In MG0011, this subject had 6 grade-1 AEs on MG0011 Days 33 through 421, in the following chronologic order—

³ American College of Gastroenterology (ACG) criteria for acute pancreatitis: “The diagnosis of AP is most often established by the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging.”

headache, hyperlipidemia, injection site bruise, nausea, oropharyngeal pain, and productive cough.

- Subject (b) (6) in 0.3 mg/kg group in the United States with GGT=582 U/L (ULN=50 U/L) on day 29 (early termination), and GGT=640 U/L a month later (safety follow-up). This was classified as a Grade-1 AE in the database. This subject's liver function was normal at screening but not baseline (GGT=286 U/L), and there was no history of liver disease. This is unexpected and suggests an error. On day 29 of zilucoplan, this subject had zilucoplan withdrawn due to increased liver enzymes. See [Figure 3](#) (ref: Applicant's narratives document).

Figure 3. Subject (b) (6) With GGT >10 x ULN (Copied from Applicant's Narratives pdf Document)
Laboratory test results for Study Participant (b) (6)

Date/ Visit	Study Day ^a	ALT (5-48U/L)	AST (8-40U/L)	ALP (40-129U/L)	GGT (10-50U/L)	Bilirubin (3-21µmol/L)
(b) (6) Screening	Day 0	23	23	89	9	<3
(b) (6) Baseline	Day 25	93	39	177	286	7
(b) (6) Week 1	Day 31	181	46	186	346	7
(b) (6) Week 2	Day 38	288	226	263	470	7
(b) (6) Early Termination (Average)	Day 52	190.5	129.5	214	434	8
(b) (6) Safety Follow-Up	Day 80	193	63	255	640	7

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase

^a The study day is calculated from the date of informed consent.

Data source(s): Listing 16.2.1.1, Listing 16.2.8.2

In Study MG0009 and MG0011, there were no subjects with liver enzymes >10X ULN.

No cases of Hy's Law were in the database. There were no serious drug-related hepatic disorders or transaminase elevations.

7.6.1.8. Vital Signs

No clinically significant changes in vital signs were noted upon review.

7.6.1.9. Subgroups

[Table 31](#) summarizes the frequency of subjects with AEs by demographic subgroup in Study MG0010. There were no significant between-group differences in the proportions of subjects experiencing AEs for any of the demographic subgroups. However, there was a small but not clinically significant difference in the proportion of females (86.5% versus 68.1%) who experienced an AE in the zilucoplan as compared to the placebo group.

Table 31. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study MG0010

Characteristic	Zilucoplan N=86 n/Ns (%)	Placebo N=88 n/Ns (%)	Zilucoplan vs. Placebo Risk Difference (%) (95% CI)
Sex, n (%)			
Female	45/52 (86.5)	32/47 (68.1)	18.5 (2.2, 34.7) *
Male	21/34 (61.8)	30/41 (73.2)	-11.4 (-32.6, 9.8)
Age group, years, n (%)			
18 to <65 years	53/64 (82.8)	47/62 (75.8)	7.0 (-7.1, 21.1)
65 to <75 years	12/21 (57.1)	14/23 (60.9)	-3.7 (-32.8, 25.4)
75 to <85 years	1/1 (100)	1/3 (33.3)	66.7 (-) **
Age group ≥65, years, n (%)			
≥65	13/22 (59.1)	15/26 (57.7)	1.4 (-26.6, 29.4)
Age group ≥75, years, n (%)			
≥75	1/1 (100)	1/3 (33.3)	66.7 (-) **
Race, n (%)			
American Indian or Alaska Native	0/0 (NA)	1/1 (100)	NA
Asian	4/7 (57.1)	9/14 (64.3)	-7.1 (-51.6, 37.3)
Black or African American	4/6 (66.7)	5/7 (71.4)	-4.8 (-55.2, 45.7)
Not Reported	2/2 (100)	1/1 (100)	0 (0, 0) **
Unknown	1/1 (100)	0/0 (NA)	NA
White	51/66 (77.3)	43/62 (69.4)	7.9 (-7.4, 23.2)
Missing	4/4 (100)	3/3 (100)	0 (-) **
Ethnicity, n (%)			
Hispanic or Latino	3/7 (42.9)	4/5 (80.0)	-37.1 (-87.9, 13.6)
Not Hispanic or Latino	56/72 (77.8)	54/79 (68.4)	9.4 (-4.6, 23.5)
Not Reported	1/1 (100)	1/1 (100)	0 (-) **
Unknown	2/2 (100)	0/0 (NA)	NA
Missing	4/4 (100)	3/3 (100)	0 (-) **
Is in United States, n (%)			
United States	36/45 (80.0)	29/43 (67.4)	12.6 (-5.7, 30.8)
Non-United States	30/41 (73.2)	33/45 (73.3)	-0.2 (-18.9, 18.6)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Double asterisk (**) indicates that counts are too small to provide a meaningful estimate of the 95% CI.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm

7.7. Key Safety Review Issues

7.7.1. Pancreatitis and Associated Pancreatic Conditions

Issue

A pancreatic safety signal was identified in the human studies, which is consistent with the nonclinical findings. There was a high incidence of pancreatic events in the 254 patient-years (330 patient-years in the 120-day update) of exposure to zilucoplan 0.3 mg/kg in these data. There were also significantly higher rates of high-lipase AEs and serum lipase elevations in the zilucoplan groups (mostly 0.3 mg/kg) compared to placebo. Pancreatic AEs did not occur during the 12-week placebo-controlled studies but only in the long-term extensions, where median time

to onset was 180 days. Because of this delayed effect, proportions of subjects experiencing pancreatic AEs (PT terms including pancreatitis, pancreatic cyst/pseudocyst, and infected pancreatic cyst/pseudocyst) could not be assessed by comparison to placebo. However, the incidence of acute pancreatitis in this program was higher than expected for the general U.S. population.

Background

The label should inform patients and providers that pancreatic conditions have occurred with the use of zilucoplan in these studies.

Nonclinical findings included elevated lipase (and amylase) and pancreatic acinar cell degeneration and inflammation (histologic focal pancreatitis). In the human studies, lipase and amylase were monitored with scheduled laboratory testing at all visits, but baseline pancreatic ultrasound was not required. Most investigators did not consider pancreatic events related to zilucoplan, and therefore did not discontinue zilucoplan when a pancreatic SAE occurred. However, there were no explicit dose-modification criteria for pancreatic or other events in these protocols. Drug discontinuation was variable. There were two deaths from pancreatic adenocarcinoma, during which zilucoplan was continued. The Applicant presented an argument that pancreatic cancer was not from zilucoplan, as it often onsets decades before presentation. However, this does not exclude a possible contributory role of zilucoplan.

Assessment

Pancreatic Adverse Events: AEs and SAEs with the terms “pancreas” or “pancreatic” in their MedDRA description.

Classic risk factors for pancreatitis are prior pancreatitis (probably the strongest risk factor) as well as gallbladder disease, excessive alcohol intake, cigarette smoking, obesity, diabetes, family history of pancreatitis, and various drugs, among others such as metabolic disease with which many of these conditions are already associated (Zhong et al. 2023). A history of any of these risk factors, none of which is as strong a predictor as prior pancreatic events, does not exclude a contributory role for zilucoplan.

In the double-blind period of Study MG0009, there were no pancreatic AEs. In Study MG0010, there were no pancreatic AEs. Pancreatic AEs did not occur in the 3-month placebo-controlled periods. In the long-term extensions MG0009 and MG0011, seven subjects experienced at least one pancreatic adverse event and all subjects were on zilucoplan 0.3 mg/kg at the time of the event.

[Table 32](#) summarizes cases of pancreatitis, pancreatic cysts, and pancreatic cancer in these studies. All occurred on a dose of 0.3 mg/kg and in the long-term extensions. This table was constructed by piecing together the narratives, ADAE and ADMH datasets, and the individual clinical study reports.

Table 32. Summary of Pancreatic AE/SAEs in the Extension Studies MG0009 and MG0011.

Pancreatic Event	Subject	Day ^a	Dose Interruption	Resolution	Prior Medical History
Pancreatitis (ERCP 1 month earlier)	(b) (6)	~840	no	yes (6 weeks later)	Metabolic syndrome

Pancreatic Event	Subject	Day ^a	Dose Interruption	Resolution	Prior Medical History
Pancreatic Cyst (1.6 cm) incidental on MRI for nephrolithiasis	(b) (6)	406	no	no	Metabolic syndrome
Larger Pancreatic Cyst (complex, 2.1 cm)		~556	no	no	Metabolic syndrome
Pancreatitis on CT scan (mild, tail, mod size pseudocyst, same region)		277	no	yes (6 weeks later)	Acute cholecystitis
Pancreatitis		77	no	unknown--discontinued from trial	None
Histologic Pancreatitis, focal chronic (biopsy)		174	no	yes--excised	Pancreatitis, metabolic syndrome
Pancreatic Cyst (benign multilocular)		141	no	no	Pancreatitis, metabolic syndrome
Worse Pancreatic Cyst (to 4.1 cm)		174	no	yes (16 days later)	Pancreatitis, metabolic syndrome
Pancreatic Cyst (appears to have been prior medical history but was recorded as an AE 4 months after screening)		45	no	no	Metabolic syndrome
Pancreatic Adenocarcinoma (advanced)		241 (mass), 312 (death)	Day before or day of surgery	FATAL	Acute pancreatitis, metabolic syndrome
Pancreatic Adenocarcinoma (advanced)		184 (mass), ~274 (death)	zilucoplan continued until day before surgery for pancreatic cancer	FATAL	Past alcohol use, past smoker, biliary stent, metabolic syndrome
Histologic inflammation on fine-needle aspirate of malignant pancreatic mass		184	no	no	Past alcohol use, past smoker, biliary stent, metabolic syndrome,

Source: Reviewer's table created based on narratives, ADAE datasets, ADMH datasets, and the individual CSRs

"~" denotes estimated days of zilucoplan by medical reviewer

Abbreviations: CT= computerized tomography scan; ERCP= endoscopic retrograde cholangiopancreatography

In [Table 32](#) there were four subjects ((b) (6)) with pancreatitis, excluding subject (b) (6) who had "marked acute inflammation" on a fine-needle aspirate of a pancreatic mass. Only one of these subjects ((b) (6)), who had a worsened pancreatic cyst SAE, had a history of a pancreatic condition before starting zilucoplan. For subject (b) (6), focal chronic pancreatitis was found on histopathology of the cyst, so this case is counted as a case of pancreatitis though subclinical prior to biopsy.

For subject (b) (6), further information was requested from the Applicant for reports, pathology results, and procedure notes. Based on the information submitted, it appears that subject (b) (6) with no history of a pancreatic condition before starting zilucoplan, developed fatal advanced pancreatic adenocarcinoma during Study MG0011 while on zilucoplan. Reportedly, no biopsy could be obtained, as the pancreatic tumor was inoperable. Zilucoplan was continued through the 2-month workup until the final diagnosis and treatment. The histology reports the Applicant submitted were for two fine-needle aspirates of the mass, which showed marked acute inflammation and atypical ductal cells. However, clinically this subject was managed as advanced pancreatic adenocarcinoma. The subject had an extremely elevated pancreatic cancer marker (CA-19) and unexplained ascites. The pancreatic tumor was considered inoperable, as it invaded celiac axis and major portal vessels. Zilucoplan was eventually discontinued, and chemotherapy for pancreatic adenocarcinoma was initiated. The subject was placed in hospice care until death seven weeks later.

There were five pancreatic cyst AEs in three subjects, and there are multiple instances in the table above for the same subject having both a pancreatic cyst and pancreatitis. One of the subjects with a pancreatic cyst had a prior history of pancreatitis before starting zilucoplan. Based on the data in [Table 32](#), the median time to first pancreatic event was 180 days. There were no pancreatic AEs in the 12-week placebo-controlled periods to allow comparison to placebo.

According to the ADMH (medical history) datasets for studies MG0009 and MG0010, six subjects had a prior history of a pancreatic condition at program enrollment before starting zilucoplan:

- Five subjects with history of pancreatitis:
 - One chronic: Subject (b) (6)
 - One acute: Subject (b) (6)
 - Three unspecified pancreatitis:
 - Subject (b) (6)
 - Subject (b) (6)
 - Subject (b) (6)
- One subject with history of pancreatic cyst:
 - Subject (b) (6)

[Table 33](#) shows the counts of subjects with a pre-existing pancreatic condition and how many experienced a pancreatic AE after being on zilucoplan.

Table 33. Relationship Between History of a Pancreatic Condition and Subsequent Pancreatic AE in MG0011

Treatment Group In Study MG0010 (n)	Counts of Pancreatic AEs in All Studies	
	AE(+)	AE(-)
History (+) (n=6)	2	4
History (-) (n=206)	5	201

As expected, a higher proportion of subjects (2 of 6) with a history of a pancreatic condition had a pancreatic-related AE in MG0011. For the six subjects with a history of a pancreatic condition prior to entering these studies (“History(+)”), two subjects had at least one pancreatic AE (“AE(+)”) and the remaining four subjects did not (“AE(-)”). Among the 206 subjects without a pancreatic history (“History(-)”), five subjects had at least one pancreatic AE (“AE(+)”) as compared to 201 subjects who did not (“AE(-)”). Therefore, 5 (2.4%) of 206 subjects without a pancreatic history experienced at least one pancreatic AE in these studies, as compared to 2 (33%) of six subjects with a pancreatic history prior to zilucoplan.

These data are consistent with the known, higher risk of a future exocrine pancreatic condition given a history of same. It does not exclude a contributory or even causative role of zilucoplan in elevating this risk. Most subjects (5 of 7 as shown in column “AE(+)”) with a pancreatic AE did not have a history of a pancreatic condition before starting zilucoplan.

In these studies, infection of a pancreatic cyst or pseudocysts occurred as a postoperative complication of endoscopic intervention for a newly identified or worsening pancreatic cyst or pseudocyst.

In the 120-day follow-up data for MG0011, another subject without a pancreatic history had a nonserious mild AE of “pancreatic steatosis” (preferred term), which is a relatively new diagnostic term for fatty infiltration of the pancreas (believed to be similar in etiology to the fatty liver associated with metabolic disease).

Adverse Events of Lipase Elevations

Lipase elevations were seen in the nonclinical studies.

Lipase is produced in the pancreas and released into the circulation from pancreatic acinar cell injury. Low-normal levels of serum lipase are not of clinical concern here, and lower limit of normal (LLN) for lipase was 0 U/L in these data at some laboratories used in Study MG0010. Although serum amylase elevation also usually occurs in pancreatitis, amylase is found in other organ systems and has a much shorter serum half-life than lipase, so it is not as sensitive or specific for pancreatitis as lipase.

Therefore, this section focuses on lipase elevations, most of which were also associated with amylase elevations.

In the double-blind period for Study MG0009, the following three subjects had AEs (non-SAEs) of high serum lipase:

- Placebo arm in the double-blind period:
 - MG0009-(b) (6): High lipase on Days 8 and 29. Medical history (MH) of hypertension and coronary artery disease.
 - MG0009-(b) (6): High lipase on Day 29. Medical history of chronic pancreatitis, obesity, and metabolic disease. Dose interrupted.
- Zilucoplan 0.1 mg/kg arm in the double-blind period: None
- Zilucoplan 0.3 mg/kg arm the double-blind period:

- MG0009- (b) (6): High lipase and amylase on Day 57. This subject was one of the two fatal pancreatic carcinoma cases.

In Study MG0009 OLE portion, the following two subjects had AEs (no SAEs) of high serum lipase (Days since first dose in MG0009 DB portion), and dose was not interrupted in either case:

- MG0009- (b) (6): High lipase on Day 140 on 0.1 mg/kg zilucoplan. Medical history noncontributory.
- MG0009- (b) (6): High lipase on Day 168 on 0.1 mg/kg zilucoplan. Also had high lipase on Day 29 of study MG0009 (see above). Medical history of chronic pancreatitis, obesity, and metabolic disease

In study MG0010, the reviewer's analysis was consistent with the Applicant's counts in Table 2 in the label and showed that 1 (1.2%) of 88 subjects on placebo and 7 (8%) of 86 subjects on zilucoplan 0.3 mg/kg had a high-lipase AE.

In study MG0011, eight subjects had nine high-lipase AEs (no SAEs), and all were on zilucoplan 0.3 mg/kg. One AE was Grade 3 (severe), three were Grade 2 (moderate), and five were Grade 1 (mild). Subject (b) (6) had two high-lipase AEs, the first of which (Day 57) resulted in interruption of zilucoplan and the last of which (Day 139) resulted in permanent discontinuation of zilucoplan.

For high-lipase AEs, of which there were 15 such AEs in this program (3 among the 6 subjects with pancreatic history, and 12 among 206 subjects without pancreatic history), it is not surprising that a pancreatic history was associated with a higher risk of high-lipase AEs on zilucoplan, although the counts are relatively small.

In the 120-day follow-up data, 9 additional subjects, none of whom had a pancreatic history, had AEs (included one SAE) of lipase elevation, and one subject had an AE of 'pancreatic steatosis' (Paul and Shihaz 2020).⁴

Adverse Events of Amylase Elevation. There were adverse events of elevated amylase in study MG0010, with 5 cases in the zilucoplan arm and 1 case in the placebo arm. There was a single, isolated high-amylase AE (not associated with an AE of high lipase) in study MG0010, and a single isolated high-amylase AE in MG0011. This examination of amylase AEs did not change the lipase assessments above.

Summary of Pancreatic and High-Lipase Adverse Events in the Three Studies

The human data suggest that zilucoplan is associated with pathologic effects on the exocrine pancreas, as do the nonclinical data. In humans, these effects include pancreatitis, pancreatic cyst/pseudocyst and/or infected pancreatic cyst/pseudocyst, and high-lipase AEs (including those >3xULN in the American College of Gastroenterology criteria for acute pancreatitis). Acinar cell damage leads to leakage of pancreatic enzymes such as lipase (and amylase) into the circulation

⁴ Pancreatic steatosis is a relatively newly recognized diagnosis involving fatty infiltration of the pancreas, and is associated with pancreatic scarring, pancreatitis, and possibly pancreatic cancer. The diagnosis of pancreatic steatosis is usually made via U/S, CT, or MRI scan

and are generally believed to lead to pancreatic cyst formation, pancreatitis, and may eventually lead to pancreatic adenocarcinoma.

In the human data, zilucoplan was associated with a higher risk of pancreas-related events in patients with a prior history of pancreatic conditions before starting zilucoplan. Two of 6 subjects with a prior pancreatic history as compared to 5 of 206 subjects without a history suffered a pancreatic event (pancreatitis or cyst) while on zilucoplan. Although a prior pancreatic history increases the risk of future events, this does not exclude a contributory role of zilucoplan.

Discontinuation of zilucoplan in pancreatic SAEs was variable. A few investigators considered pancreatic and lipase AEs to be 'related' to zilucoplan, but most did not. Consequently, zilucoplan was not interrupted during most pancreatic adverse events, including the two deaths from pancreatic adenocarcinoma.

Pancreatitis and pancreatic cysts (newly identified or increased in size while on zilucoplan) did occur in 6 (3%) of 213 subjects, which is high for a program this size (330 patient-years including 120-day update) in myasthenia gravis, a disease not classically associated with pancreatitis or pancreatic cysts. Baseline pancreatic ultrasound was not a scheduled procedure but could have been very useful in assessing the rate of new pancreatic cyst formation and changes in prior cysts. For acute pancreatitis cases only (n=3 which excludes subject (b) (6) with histologic chronic pancreatitis) during the 330 patient-years of the data submitted for MG, the incidence translates to 900 cases per 100,000 patient-years. This rate is considerably higher than the incidence of acute pancreatitis in the general population of the United States, which is 5 to 35 cases per 100,000 person-years (Vege 2023).

Of the six subjects with a prior medical history of pancreatitis or pancreatic cyst before starting zilucoplan, two (33%) had an episode of pancreatitis during these studies. Two subjects died of pancreatic adenocarcinoma within two months of diagnosis, one with and one without a pre-zilucoplan history of a pancreatic condition. Given the rarity of acute pancreatitis in the general population (5 - 35 in 100,000 patient-years), the probability of having three subjects develop acute pancreatitis in this small MG population of about 254 patient-years (330 including the 120-day data) is high.

In most cases, zilucoplan was not interrupted for high-lipase or the occurrence of pancreatic events in these studies. In one case where pancreatitis was not diagnosed despite months of abdominal symptoms, foci of focal chronic pancreatitis were discovered on histology, and this was not listed as an AE of pancreatitis. Additionally, in only a few cases did investigators consider pancreatic-related issues to be "related" to zilucoplan, and even in those few cases, zilucoplan was not necessarily discontinued.

Consistent with the pancreatic adverse events in the extension studies, a significantly higher rate of high-lipase AEs and laboratory elevations of serum lipase occurred in the zilucoplan 0.3 mg/kg group compared to placebo. Additionally, mean serum lipase level at scheduled visits increased by 44 U/L, and there were more cases of lipase values >3xULN in the zilucoplan 0.3 mg/kg group than the placebo group (no change in mean lipase) beginning at day 57 and beyond.

It is possible that zilucoplan has a complement-mediated adverse effect on the exocrine pancreas not shared by the antibody C5 inhibitors, and it may be related to effect on pancreatic

complement C3 activity. There is also a possibility, but not proven, that the mechanism of action of zilucoplan unlike the biologic C5 inhibitors may involve complement-mediated pancreatic acinar cell injury. Complement C5 appears to exert an anti-inflammatory effect on the pancreas in animals and humans (Bhatia et al. 2001). On the other hand, C3a (part of the C5 cleavage complex) is inflammatory to the pancreas, as it is associated in humans with the severity of subsequent acute pancreatitis following first onset of symptoms a week earlier (Gloor et al. 2003). The effect of C5 inhibition by zilucoplan on levels of C3 and C3a (upstream), C5 and C5b levels in the pancreas, and on potential pancreatic inflammatory effects does not seem to have been investigated in this program or elsewhere. Complement levels and activity of C5, C5a, C5b, C3, C3a, and others and their effects on the pancreas were not assessed in this program.

The product labeling will describe the risk of pancreatitis and other pancreatic events that were seen in these studies. For inclusion in Section 5 (Warnings and Precautions), there needs to be “reasonable evidence of a causal association, but a causal relationship need not to have been definitively excluded” (Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format). Although pancreatic events were not observed during the three-month duration of the placebo-controlled studies, a causal relationship cannot be definitively excluded based on the nonclinical findings and the high incidence of pancreatic events observed in the long-term data in this program.

Conclusion

Pharmacovigilance. The Applicant will be requested to perform postmarketing surveillance for serious events related to pancreatitis and other pancreatic adverse events.

Labeling. Pancreatitis and other pancreatic conditions as well as lipase and amylase elevations will be added to the Warnings and Precautions section of the label. The following considerations must be conveyed to patients and providers in the labeling before using zilucoplan:

1. Patients and providers should be made aware of the risk of pancreatic events while on zilucoplan. A warning in Section 5 and further description in section 6 will be included. Patients and providers should have a lower threshold for stopping zilucoplan and pursuing a workup for pancreatic disease, if symptoms occur that are suggestive of pancreatitis (e.g., nausea, vomiting, abdominal pain, left shoulder pain, back pain, epigastric pain, and/or weight loss, among others).
2. If acute (or exacerbations of chronic) pancreatitis or pancreatic cyst develop while on zilucoplan, the provider and patient should consider whether the benefit outweighs the risk of continuing zilucoplan.

7.7.2. Meningococcal Infection

Issue

Susceptibility to infection with encapsulated organisms such as *Neisseria meningitidis* secondary to C5 inhibition.

Background

C5 inhibitors increase the risk of infection with encapsulated organisms such as *N. meningitidis*. For the other approved C5 inhibitors, there is a boxed warning and REMS for serious meningococcal infections, which may be fatal especially if not treated early. Therefore, meningococcal vaccination and antibiotic prophylaxis are key considerations for starting patients on these drugs.

Assessment

No cases of infection with *N. meningitidis* or *N. gonorrhoeae* were reported in these data.

Conclusion

This issue will be addressed in labeling and with a REMS, to harmonize with the other C5 inhibitors.

We note that patients receiving complement inhibitors remain at risk for meningococcal disease even after meningococcal vaccinations (Mbaeyi et al. 2020). In addition, as noted in the consultative review provided by the Division of Vaccines and Related Product Applications/Office of Vaccines Research and Review/CBER (CBER/OVRR/DVPRA/CRB3) dated August 9, 2023, the role of antimicrobial prophylaxis is poorly defined in this patient population without clear recommendations regarding the choice of antimicrobials, timing of prophylaxis relative to vaccination or duration of therapy. The benefit-risk profile of antimicrobial prophylaxis in individuals at high risk for meningococcal infection is also poorly defined, as antimicrobial prophylaxis may not prevent all cases of meningococcal disease and may be associated with an increased risk of antimicrobial resistance. In the absence of appropriately designed clinical studies, the role and best practices for antimicrobial prophylaxis in individuals receiving complement therapy with or without meningococcal vaccination is unknown. The labeling regarding vaccination and antibiotic prophylaxis is in agreement with recommendations provided by CBER/OVRR/DVPRA/CRB3 and by the Division of Anti-Infective (DAI) in a consult dated August 18, 2023. The Applicant will be requested to perform pharmacovigilance for infection, including meningococcal infection and opportunistic infection, and to submit quarterly analyses.

7.7.3. Other Serious Infections

Given the mechanism of action, there may be a theoretical risk of other serious infections associated with zilucoplan.

One subject on zilucoplan 0.3 mg/kg developed *Candida* endocarditis on day 353, preceded nine months earlier (on Day 71) by bacteremia (*Acinetobacter*, *Brevibacterium*, and *Corynebacterium*), and followed 5 months later (day 503) by staphylococcal bacteremia. This subject was a 71-year-old male with a very complex medical history and very high risk of immunosuppression, including insulin-dependent diabetes mellitus and long-term corticosteroids and antibiotics before and during zilucoplan administration.

A few pancreatic infections were reported, which involved pancreatic cysts/pseudocysts, liver, and/or the peripancreatic or perihepatic spaces, although not from unusual organisms or under unexpected circumstances. Urinary tract infection occurred more often in the zilucoplan than

placebo group in study MG0010, which was not included in the proposed USPI, but at low rates (8% versus 5%). No other unexpected, serious infections occurred in subjects on zilucoplan.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Renal Impairment

A renal impairment study (UP0114) assessed the pharmacokinetics of zilucoplan and its metabolites (RA103488 and RA102758) after administration of a single subcutaneous dose of 0.3 mg/kg (weight-band based dosing) in subjects with severe renal impairment (estimated creatinine clearance <30mL/min based on Cockcroft-Gault formula) and matched healthy subjects with normal renal function. Zilucoplan maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC_{0-inf}) was 8% and 13% lower in subjects with severe renal impairment subjects respectively as compared to subjects with normal renal function. Whereas, for metabolite RA102758, C_{max} and AUC_{0-inf} was 12% and 10% lower in subjects with severe renal impairment respectively as compared to subjects with normal renal function. For RA103488, another metabolite, AUC_{0-inf} and C_{max} was 1.4- to 1.5-fold higher in subjects with severe renal impairment respectively as compared to subjects with normal renal function.

For zilucoplan and RA102758, the PK is generally similar across two populations. Based on study UP0113 (zilucoplan dose of 0.3 mg/kg once daily for 14 days), the exposure of RA102758 and RA103488 is approximately 10% of zilucoplan exposure. Due to much lower exposure of RA103488 compared to zilucoplan, the Applicant concludes that the clinical impact of the observed increase in exposure for RA103488 is expected to be negligible. It is also noted that the increase in total C5 concentration at day 3 and day 6 was similar between subjects with normal renal function and subjects with severe renal impairment. Based on urine analysis in the study, zilucoplan and both metabolites are minimally renally excreted in both the normal and severe renal impairment subjects (<1% of dose in total across all analytes).

Overall, the review team agrees with the Applicant's conclusion that severe renal impairment did not influence PK and PD of zilucoplan. The review team agrees with the proposed labeling that no dose adjustment is required in patients with renal impairment. For further details, refer to Section [14.2.3](#).

8.1.2. Hepatic Impairment

A hepatic impairment study (UP0094) assessed the pharmacokinetics of zilucoplan and its metabolites (RA103488 and RA102758) after administration of a single subcutaneous dose of 0.3 mg/kg (weight-band based dosing) in subjects with moderate hepatic impairment (Child-Pugh category B with a score of 7 to 9) and matched healthy subjects with normal hepatic function.

Zilucoplan peak exposure C_{max} was similar in subjects with moderate hepatic impairment and normal hepatic function (geometric LSM ratio [90% CI] - 0.95 [0.82, 1.10]). However, the

systemic exposure based on AUC_{0-last} and AUC_{0-inf} was 24% lower in subjects with moderate hepatic impairment compared with subjects with normal hepatic function (geometric LSM ratio [90% CI] - 0.76 [0.65, 0.88]). The peak exposure C_{max} for RA102758 and RA103488 increased by 21% and 16% respectively in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. Whereas the systemic exposure AUC_{0-last} for RA102758 and RA103488 increased by 9% and 22% respectively in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. There was no meaningful difference identified with respect to total C5 levels and complement inhibition (sRBC lysis) between moderate hepatic impairment subjects and normal subjects despite a 24% lower zilucoplan systemic exposure in moderate hepatic impairment subjects.

Overall, the observed decrease in systemic exposure of zilucoplan in moderate hepatic impairment subjects is not expected to be clinically significant. The review team therefore agrees with the proposed labeling that no dose adjustment is required in patients with mild and moderate hepatic impairment. The Applicant will be recommended to include the following in section 12.3 of labeling “The pharmacokinetics of zilucoplan in patients with severe hepatic impairment have not been studied.” For further details, refer to Section [14.2.4](#).

8.1.3. Ethno-Bridging Study

An ethnobridging study (UP0113) assessed the PK and PD of single and multiple doses of zilucoplan in healthy Japanese and white subjects. The Applicant noted that the peak exposure, C_{max} , and the systemic exposure (AUC) of zilucoplan and metabolites (RA102758 and RA103488) were generally similar in Japanese and white subjects following a single (0.1 mg/kg or 0.3m/kg) and multiple (0.3 mg/kg for 14 days) doses of zilucoplan. The Applicant also noted that the extent and duration of PD response (total C5 levels and %sRBC Lysis Inhibition) appeared to be similar between Japanese and white subjects. The Applicant therefore concludes that zilucoplan dose adjustment for Japanese and white subjects is not warranted. It is noted that any labeling claim based on the above ethnicity assessment is not made by the Applicant. For further details, refer to Section [14.2.2](#).

8.1.4. Body Weight

A body weight-band based dosing was followed throughout the clinical development program of zilucoplan. The proposed weight-band dosing regimen ([Table 8](#)) is consistent with the weight-band dosing regimen evaluated in Phase 3 (MG0010) study ([Table 9](#)). Based on population PK analysis, it was confirmed that body weight is a significant covariate, and the simulation further supports the body weight-band based dosing regimen (Section [14.5](#)). Further, the review team evaluated the need for removing the cap for the upper body weight limit proposed in the initial labeling submission (i.e., dosing for patients weighing higher than 150 kg) based on the response to FDA labeling edits (submitted by email dated August 14, 2023). The proposed fixed dose for patients with weight 150 kg and above is 32.4 mg same as the fixed dose for patients with weight ranging from 77 kg to <150 kg.

The simulation of steady state exposures for patients records in the National Health and Nutrition Examination Survey (NHANES) database were conducted by the Applicant utilizing the validated population PK model and proposed dosing regimen as function of body weight. The

Applicant concluded that simulated exposures are comparable across weight ranges of 25 kg to 150 kg for all 3 dosing categories ([Figure 16](#) of Section [14.5](#)). Despite the variability in PK associated with body weight, there was comparable efficacy outcome (mean change from baseline for MG-ADL score) across the evaluated body weight categories ([Figure 21](#) of Section [14.5](#)) in Phase 3 study (MG0010) providing further support for the use of body weight-band based dosing regimen.

Further, the Applicant referred to 5 subjects with weight greater than 150 kg from the Phase 2 and open-label (OL) extension study who were on the fixed dose of 32.4mg, which was the same dose for patients with weight 77 kg to 150 kg. From these 5 subjects, 2 subjects were from Phase 2 study (MG0009); and 3 subjects were from OL extension study (MG0011; who switched from placebo in MG0010 study to 0.3 mg/kg dose (fixed dose of 32.4mg) in MG0011 study) ([Table 34](#)). Based on these data and simulations of PK exposures for subjects above 150, the review team concluded that steady state exposures for zilucoplan were comparable for subjects weighing > 77 kg with the 32.4 mg dose [Figure 4](#). In addition, the observed sRBC lysis inhibition was >95% in subjects with body weight 77 to 171 kg with the 32.4 mg dose which suggests comparable PD response across the different body weights. Based on the above, the review team therefore agrees with the body weight-band based dosing regimen presented in Table 8.

Table 34. Subjects of Weight >150kg in MG0009, MG0010, and MG0011

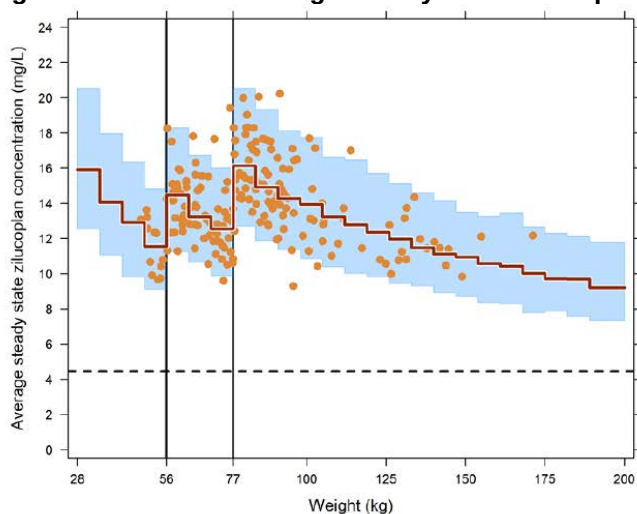
Study participant ID	Weight category**	Actual weight (kg)	Enrolled study	Study for 0.3mg/kg exposure	Actual dose
(b) (6)	≥150kg	171.1	MG0009	MG0009	32.4mg
	≥150kg	155	MG0009/MG0011	MG0009/MG0011	32.4mg
	≥150kg	157.3	MG0010/MG0011	MG0011	32.4mg
	≥150kg	166	MG0010/MG0011	MG0011	32.4mg
	≥150kg	169	MG0010/MG0011	MG0011	32.4mg
	≥150kg	153*	MG0010/MG0011	MG0010/MG0011	32.4mg

* The patient with baseline weight 144kg in MG0010 and 153kg in MG0011, not included in Pool S1A, S1B, E1 and E2.

** No patient weighing 150kg in weight category ≥150kg.

Data source: MG0009, MG0010, MG0011 (120 Day safety cutoff) Listing 16.2.5.3

Source: Table 1 of UCB Position on ZILBRYSQ Dose for Upper Body Weight (sent by email on 14 August 2023)

Figure 4. Predicted Average Steady State Zilucoplan Concentration by Weight

Note: Red line and blue area: median and 90% of simulated values. Orange circles: individual predicted values.

Vertical black lines: weights (56 and 77kg) where dose changes from 16.6mg to 23mg to 32.4mg).

Date source: Modeling and simulation report CL0508; Figure 24, page 56.

Source: Figure 1 of UCB Position on ZILBRYSQ Dose for Upper Body Weight (sent by email on 14 August 2023)

8.1.5. Other Intrinsic Factors

The population PK analyses indicated that zilucoplan PK was not affected by age, sex, or race (Section [14.5](#)). Therefore, no dose adjustment is warranted based on these factors.

The Applicant also evaluated the relative bioavailability of zilucoplan at 0.3 mg/kg single dose following subcutaneous administration at different injection sites (abdomen [reference site], thigh, and upper arm) in healthy subjects. There were no notable differences in peak (C_{max}) and systemic (AUC_{0-t}) exposure of zilucoplan between abdomen and arm injection sites or between abdomen and thigh injection sites. For both C_{max} and AUC_{0-t} , the geometric least squares mean ratio for the comparison of arm versus abdomen and thigh versus abdomen was close to 1 with 90% CI within criteria of 80% to 125%. The review team therefore agrees with the proposed labeling that “Administer ZILBRYSQ subcutaneously into areas of the abdomen, thighs, or back of the upper arms.” For further details, refer to Section [14.2.5](#).

8.2. Extrinsic Factors

8.2.1. Drug Interactions

Zilucoplan is a 15-amino acid macrocyclic peptide; hence in vivo degradation into smaller peptide fragments and amino acids by nonspecific proteases is likely. Hydrolysis and terminal ω -oxidation were identified as the two major metabolic pathways of zilucoplan resulting in the formation of RA102758 and RA103488, respectively. RA102758 is formed by protease mediated degradation of the c terminal lysine residue attached to the ethylene glycol-palmitoyl tail. The metabolite RA103488 is formed by ω -hydroxylation on the palmitoyl tail of intact zilucoplan majorly by cytochrome P450 (CYP) 4F2 (minor contribution by CYP4A11,

CYP4F3A, and CYP4F3B). The exposure of the aforementioned two metabolites is low compared to zilucoplan (i.e., ~10% of the zilucoplan exposure at steady state).

In vitro studies have shown that zilucoplan is not a substrate of major cytochrome P450 (CYP450) enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A) and transporters (P-gp, BCRP, OATP1B1, OATP1B3). In vitro studies also suggested lack of potential for zilucoplan to inhibit or induce CYP450 or inhibit uridine diphosphoglucuronosyl transferases or inhibit major transporters. From the results of in vitro drug interaction testing, the Applicant concluded that clinically relevant interactions between zilucoplan and substrates of major CYP450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A, and 4F), uridine diphosphoglucuronosyl transferases (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15), and transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2-K, OCT1, and OCT2) is unlikely (Section [14.1](#)). Clinical drug-drug interaction (DDI) studies were therefore not conducted.

For gMG patients, concomitant medications that inhibit/induce CYP4F2 are unlikely. Further, CYP4F2 is majorly involved in disposition of endogenous long-chain fatty acids and is not known as a major CYP enzyme contributing to disposition of many prescription drugs. Therefore, for zilucoplan, clinical DDI victim study with CYP4F2 perpetrator is not necessary. Additionally, there is no established CYP4F2 perpetrator/inhibitor that can be used for victim study for CYP4F2 substrate. Based on the above, a clinical DDI study for zilucoplan is not warranted.

Overall, due to its lack of interactions with transporters and major CYP enzymes in vitro, the potential of zilucoplan for drug interactions is low; therefore, no dose adjustments are proposed for use of zilucoplan with concomitant medications. The review team agrees with the Applicant's conclusions.

8.3. Plans for Pediatric Drug Development

Zilucoplan was granted orphan drug designation; therefore, pediatric assessments under the Pediatric Research Equity Act are not required. However, the Applicant has submitted protocols for pediatric studies.

8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential

There are limited data for the use of zilucoplan in pregnant and lactating women, as subjects of childbearing potential were required to use a highly effective method of birth control, and the study drug was discontinued if subjects were pregnant per the protocol.

There was one subject (b) (6) who became pregnant as of the clinical cutoff date. The pregnancy occurred in a subject who was on placebo in the double-blind phase of Study MG0009, and zilucoplan 0.1 mg/kg in the MG0009 extension. Reportedly, zilucoplan was discontinued one day after the last menstrual period. The subject was exposed to zilucoplan for "more than a year." The pregnancy was complicated by gestational diabetes, and the infant was delivered by elective C-section at full term. By the time of follow-up of the infant at about 16

months of age, there were no reported congenital malformations, failure to thrive, or developmental delay.

In an enhanced pre- and postnatal development study with an embryofetal component in cynomolgus monkeys, SC administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) to pregnant dams from GD 20 through 100 produced no adverse effects on pregnancy outcome or embryofetal development in groups evaluated on PND 100, but in the groups dosed from GD 20 through birth, there was an increase in prenatal loss (spontaneous abortion and unscheduled C-section due to intrauterine death) in all treatment groups compared to C (6.25, 31.25, 25, and 31.25% pregnancy loss in C, LD, MD, and HD groups, respectively). Complement inhibition was similar at all doses throughout the dosing period, which could account for the lack of a dose-response. At the low-effect dose for increased embryofetal mortality, the maternal plasma exposure (AUC) was 230 ug.h/mL.

In a male fertility study in the cynomolgus monkey, SC administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) for 13 weeks did not produce mortality, clinical signs, or effects on BW, testicular size, clinical pathology, immunophenotyping, or organ weights. Testicular germ cell depletion/degeneration was observed in treated animal from all dose groups at the terminal and recovery sacrifices, although not with a dose-related incidence or severity. The finding was said to be consistent with a spontaneous background lesion, but since it only occurred in drug-treated animals, relationship to drug cannot be dismissed. Inhibition of complement-dependent hemolysis was maintained throughout the dosing period at similar levels in all treatment groups. At the LOAEL for germ cell degeneration, exposures (AUC) were 227 and 488 ug.hr/mL on days 1 and 91, respectively.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 216834 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess. As such OPQ recommends approval of this NDA from a quality perspective.

For additional details, refer to the OPQ Integrated Quality Review dated June 6, 2023, and review addendum dated August 23, 2023.

9.1. Device or Combination Product Considerations

The Center for Devices and Radiological Health (CDRH) was consulted for the syringe and needle safety device. The CDRH review, dated May 8, 2023, recommends approval of the application.

10. Human Subjects Protections / Clinical Site and Other Good Clinical Practice Inspections / Financial Disclosure Review

The results of the clinical site inspections support the conclusion that the studies were conducted adequately, and that the data generated support the proposed indication. Review of the financial disclosures did not raise concerns about the validity or reliability of the data.

11. Advisory Committee Summary

Not applicable.

III. Additional Analyses and Information

12. Summary of Regulatory History

Zilucoplan (also referred to as RA101495), is a macrocyclic peptide that is intended to inhibit complement activation at the level of complement component 5 (C5) by binding to C5 and preventing cleavage into C5a and C5b. Ra Pharmaceuticals submitted the initial IND 134340 on September 1, 2017, and the IND became active on September 29, 2017, for the treatment of generalized myasthenia gravis (gMG).

In the end-of-phase 2 (EOP2) meeting preliminary comments, dated March 29, 2019, the Agency provided advice on dosing regimen, endpoint selection, immunogenicity assessment, drug-drug interaction assessments, metabolites, and recommendations on the human factors validation and use-related risk analysis.

Orphan drug designation was granted on August 26, 2019, for the treatment of myasthenia gravis. With the orphan drug designation, the Applicant was exempt from Pediatric Research Equity Act requirements.

(b) (4)
The Applicant submitted a human factors validation protocol for review on December 20, 2019. An advice letter detailing issues and recommendations on the human factors validation study protocol was provided on February 14, 2020.

A proprietary name review request for “Zilbrysq” was submitted to the IND on July 14, 2020, and the name was determined to be conditionally acceptable on December 22, 2020. The same proposed proprietary name was submitted to the initial NDA.

Type C written responses were provided on September 13, 2021, providing guidance and advice on the statistical analysis plan for the Phase 3 MG0010 study and the integrated statistical analysis plan.

The Agency notified the Applicant in an email on August 16, 2021, that the Applicant will need to conduct an in vivo micronucleus assay and provide a weight-of-evidence assessment of the carcinogenic potential of zilucoplan at the time of NDA submission. The micronucleus assay and carcinogenicity assessment were submitted in the initial NDA.

A Type B, pre-NDA meeting was scheduled for May 5, 2022, and subsequently cancelled by the Applicant since the Applicant had no additional questions or clarifications of the May 3, 2022, preliminary comments. In the preliminary comments, the Division requested that the Applicant clarify how they intended to meet the substantial evidence of effectiveness standard with a single pivotal study.

In the pre-NDA meeting package, the Applicant proposed a safety database of 84 patients exposed for at least 12 months of the proposed dose (0.3 mg/kg/d); however, the Division typically requires a minimum of 100 patients for a rare disease such as gMG. In an email correspondence on May 4, 2022, the Applicant proposed safety data for 90 gMG patients with at

least 1 year of exposure at the time of initial NDA submission and an estimated 38 gMG patients at the 120-day safety update.

Although the proposed Risk Evaluation and Mitigation Strategy (REMS) to mitigate the potential risk of meningococcal infection was not submitted with the pre-NDA document, the Agency provided recommendations what to include in the proposed REMS in the NDA. The proposed REMS was submitted with the initial NDA.

The original NDA was submitted on August 31, 2022, and filed on October 30, 2022, with no filing issues identified.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The in vitro metabolic profiling of zilucoplan indicated that in addition to parent, 6 metabolites were produced in monkey and human hepatocytes. No human unique metabolite was observed. In vivo, two major metabolic pathways, hydrolysis, and terminal ω -oxidation, resulted in the formation of RA102758 and RA103488, respectively, in similar proportions in monkey and human plasma. These metabolites are covered in the monkey toxicity studies; however, according to the FDA clinical pharmacology reviewer, there are no major human metabolites.

Based on the pharmacologic and metabolic similarity to humans, the cynomolgus macaque was considered the most relevant species for toxicity testing; therefore, nonclinical safety assessment in two species was not required by the Division. Repeat-dose toxicity studies consisted of 4-week SC studies in the rat and cynomolgus monkey and 13- and 39-week SC studies in the monkey. In the 4-week rat study, adverse effects were limited to injection site reactions at the HD (40 mg/kg/day). In the 4-week monkey study (0, 1, 2, or 4 mg/kg/day), elevated bile acids and lipase and peribiliary mixed cell inflammation in the liver were observed at the MD and HD. Widespread inflammatory effects and liver and pancreas histopathology were highlighted in the reviews of the 13-week monkey study (0, 0.25, 1, 2, or 10 mg/kg/day). In the pharmacology/toxicology review under (b) (4) (Rama Guidi, Ph.D., December 29, 2016), the histopathological changes observed in the 13-week study included:

...marked inflammation (vasculitis), mild pancreatic acinar degeneration, mild ductular hyperplasia, and degeneration of the pancreas in one male monkey administered 10 mg/kg/day, and minimal pancreatic acinar degeneration at ≥ 1 mg/kg/day in females. Moderate mucosal vesicular degeneration of the tongue was present in two 10 mg/kg/day males, one of which had minimal neutrophilic inflammation of the tongue mucosa in an area of vesiculation. Minimal vascular/perivascular mononuclear cell infiltration of the tongue and urinary bladder was observed at 0.25 mg/kg/day. Vascular/perivascular mononuclear cell infiltration showed partial recovery, however microscopic changes in the pancreas and liver at 10 mg/kg/day did not fully resolve after 4 weeks of observation.

According to the pharmacology/toxicology review under (b) (4) (Wei Sun, Ph.D., April 22, 2019):

There were RA101495-related clinical signs for males in the high dose [10 mg/kg/day] group that included reddened and dry face, bilateral ocular discharge with periorbital redness and dry face, slight facial jaundice (icterus), and abdominal pain. Increased ALT, ASP, ALP, GGT, creatine kinase, total bilirubin, lipase, and bile acids were observed in males from the 10 mg/kg/day group. These findings, with particular reference to bilirubin, appeared to correlate with findings of slight facial jaundice (icterus). Potential target organs of toxicity included the tongue (moderate mucosal vesicular degeneration of the tongue for males at 10 mg/kg/day), pancreas (marked vascular/perivascular mononuclear cell inflammation (vasculitis), mild pancreatic acinar degeneration, and mild ductular hyperplasia for males at 10 mg/kg/day), and multi-organ mononuclear infiltrates observed in the pancreas, kidney, tongue, esophagus, salivary gland, thyroid, rectum, stomach, and urinary bladder for all drug treated groups. ...The marked vascular/perivascular mononuclear inflammation (vasculitis) in the pancreas at the high dose of 10 mg/kg/day was considered adverse and dose-limiting.

These observations are consistent with the findings in the 39-week monkey study (0, 0.25, 1, 2, 4, or 6 mg/kg/day) in which all doses were associated with swelling, ocular discharge, reddened skin, dose site reactions, and inflammatory cell infiltrates of most organs. Mononuclear and/or mixed cell interface infiltrates and epithelial vesicular degeneration/erosions/necrosis were prominent in the tongue, cervix, vagina, esophagus, stomach, and skin. Other microscopic findings included salivary gland duct degeneration/regeneration, uterine endometrial degeneration, increased cellularity of the thymus, and epithelial vesicular degeneration in the cervix. In 3 animals that were sacrificed early due to moribund condition (LD animal 2501 on Day 245 with colitis, MHD (4 mg/kg) and HD animals 5003 and 6503 on Days 52 and 203 with skin ulcerations and erosions) histopathology findings included liver fibrosis and lung edema (5003) and moderate pancreatic acinar degeneration (all 3 animals) or pancreatic duct degeneration/regeneration with acinar atrophy (2501), with associated increases in amylase and lipase at the 2 highest doses. Pancreatic acinar cell degeneration with fibrosis/fibroplasia was also found in 1 MD (2 mg/kg) animal (4003) at the scheduled terminal sacrifice. After the recovery period, inflammatory cell infiltration had regressed in most organs, but mucosal infiltrates of the esophagus, squamous metaplasia of the cervical mucosa, increased medullary cellularity in the thymus, and lymphoid follicles or aggregates in the bone marrow remained, although decreased in incidence and/or severity. A NOAEL was not established, but the highest tolerated dose was considered to be 2 mg/kg/day, which was associated with an exposure (AUC_{0-24}) of 541 $\mu\text{g}\cdot\text{h}/\text{mL}$ for combined sexes on Day 273, approximately 2X the maximal anticipated clinical exposure (approximately 275 $\mu\text{g}\cdot\text{h}/\text{mL}$ at 32.4 mg).

The pancreatic infiltrates and degeneration, lymphoid hypercellularity, and sporadic bridging bile duct hyperplasia and hepatic fibrosis observed the monkey studies were thought to be secondary to pathogen proliferation, colonization, and infection resulting from immunosuppression caused by pharmacologic inhibition of C5. Opportunistic pathogens were isolated in cultures collected from 2 animals sacrificed prematurely in the 39-week monkey study. Since blocking C5 cleavage prevents the formation of the terminal pathway products C5a and C5b-9, this would be expected to increase the risk of infections.

Zilucoplan was negative for genotoxicity in in vitro (Ames and human lymphocyte) and in vivo (rat micronucleus) assays. No carcinogenicity studies were conducted, as agreed to by the Division, because of the lack of pharmacological activity in rodent species.

In a male fertility study in the cynomolgus monkey, SC administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) for 13 weeks did not produce mortality, clinical signs, or effects on BW, testicular size, clinical pathology, immunophenotyping, or organ weights. Testicular germ cell depletion/degeneration was observed in treated animal from all dose groups at the terminal and recovery sacrifices, although not with a dose-related incidence or severity. The finding was said to be consistent with a spontaneous background lesion, but since it only occurred in drug-treated animals, relationship to drug cannot be dismissed. Inhibition of complement-dependent hemolysis was maintained throughout the dosing period at similar levels in all treatment groups. At the LOAEL for germ cell degeneration, exposures (AUC) were 227 and 488 ug.hr/mL on Days 1 and 91, respectively.

In an enhanced pre- and postnatal development study with an embryofetal component in cynomolgus monkeys, SC administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) to pregnant dams from GD 20 through 100 produced no adverse effects on pregnancy outcome or embryofetal development in groups evaluated on PND 100, but in the groups dosed from GD 20 through birth, there was an increase in prenatal loss in all treatment groups compared to C (6.25, 31.25, 25, and 31.25% pregnancy loss in C, LD, MD, and HD groups, respectively). Complement inhibition was similar at all doses throughout the dosing period, which could account for the lack of a dose-response. At the low-effect dose for increased embryofetal mortality, the maternal plasma exposure (AUC) was 230 ug.h/mL.

The nonclinical studies completed for the NDA are considered adequate to support approval. The reproductive (testicular germ cell depletion/degeneration) and developmental (increased prenatal loss) effects observed in monkeys should be described in labeling.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Repeat-Dose Toxicity

Table 35. Study Title: A 39-Week Toxicity Study of RA101495 by Subcutaneous Injection in Cynomolgus Monkeys With an 8-Week Recovery Period

Description	Parameter
Study no.:	20086030
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11 Feb 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, batch #, purity:	RA101495, 7002753, 94.2%

Source: Study report

Table 36. Study Methods

Methods	Parameter
Doses:	0 (vehicle), 0.25, 1, 2, 4, or 6 mg/kg/day
Frequency of dosing:	QD
Route of administration:	Subcutaneous
Dose volume:	0.2 mL/kg
Formulation/Vehicle:	??
Species/Strain:	Monkey / Cynomolgus
Number/Sex/Group:	3/sex/group main + 2/sex/group recovery
Age:	2.6 to 3.9 years
Weight:	2.3 to 3.3 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that impacted study quality or integrity

Source: Study Report

Table 37. Experimental Design

Group Nos.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study ^a		Recovery Study ^b	
					Males	Females	Males	Females
1	Control	0	0.2	0	3	3	2	2
2	RA101495	0.25	0.2	1.25	3	3	0	0
3	RA101495	1.0	0.2	5.0	3	3	0	0
4	RA101495	2.0	0.2	10.0	3	3	2	2
5	RA101495	4.0	0.2	20.0	3	3	2	2
6	RA101495	6.0	0.2	30.0	3	3	2	2

^a Main study necropsy was Day 274 for the animals indicated with the following exceptions: one Group 5 male was euthanized early on Day 52; one Group 6 female was euthanized early on Day 203; one Group 2 female was euthanized early on Day 245.

^b Recovery necropsy was Day 330.

Source: Text Table 3 (Page 24) in 4.2.3.2 Study No. 20086030 Amended Final Report 2

The following endpoints were evaluated: clinical signs, BW, food consumption, veterinary physical examinations, cardiac (ECG, BP, and HR), ophthalmology, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), ADA (direct enzyme-linked immunosorbent assay), TK, organ weights, and gross and microscopic findings.

Observations and Results

Mortality

Single animals from the 2 highest dose groups were sacrificed early (Days 52 and 203) due to multifocal skin erosions and/or ulcerations. A single LD animal was sacrificed on Day 245 due to weight loss, liquid feces, abdominal pain, and anorexia that correlated histologically with chronic ulcerative colitis and proctitis.

Clinical Signs

Clinical signs included swelling, ocular discharge, reddened skin, injection site reactions, and various lesions or abrasions, which were observed in all treatment groups. Dose holidays were given for 1 MHD animal and 1 HD animal from Days 148 to 152 for buccal mucosa erythema and oral ulceration which resolved by Day 152.

Body Weights

There were no drug-related changes in BW, except in the LD animal (2501) that was sacrificed early.

Cardiovascular

There were no effects on cardiovascular endpoints.

Ophthalmology

One HD male (6504) had diffuse conjunctival swelling and conjunctival hyperemia on Days 69 and 268 that resolved after the 8-week recovery period. Gingivitis was also noted concurrently in this animal. Dose-dependent drug concentrations were measured in the tear and salivary fluid, and HD animals had concentrations high enough to inhibit local C5. Therefore, the immune response in the mucous membranes of the eye and oral cavity may have been compromised.

Clinical Pathology

Hematology

There were no drug-related changes in hematology or coagulation parameters.

Clinical chemistry

Drug-related findings included increased amylase and lipase in individual animals (5002, 5003, 6503) at the 2 highest doses. In the 1 MHD male (5003) that was sacrificed prematurely, clinical chemistry changes (increased liver enzymes, bilirubin, and bile acids) correlated with histopathology findings in the bile duct and liver (bridging portal fibrosis with biliary hyperplasia, portal mononuclear cell infiltrates, and edema of the liver).

Urinalysis

There were no changes in urinalysis parameters.

Complement Activity

Suppression of hemolysis was observed throughout the dosing period at all doses, returning to normal during the recovery period.

ADA

Serum collected during the dosing and recovery periods was negative for anti-drug immunoreactivity.

Toxicokinetics

TK data are shown in [Table 38](#).

Table 38. TK Parameters in Monkeys

Gender:	Males					Females				
RA101495 Dose (mg/kg/day):	0.25	1.0	2.0	4.0	6.0	0.25	1.0	2.0	4.0	6.0
Parameter (Units)	Day 1									
AUC(0-t) (ng*h/mL)	59,700	193,000	348,000	632,000	1,110,000	60,200	185,000	360,000	688,000	1,040,000
C _{max} (ng/mL)	3100	12,200	21,400	37,700	66,300	3140	12,200	23,600	42,700	63,000
T _{max} (h)	3.3	2.0	2.4	3.6	3.6	2.0	2.7	2.0	3.6	3.2
	Day 182									
AUC(0-t) (ng*h/mL)	118,000	327,000	635,000	1,250,000† ⁴	2,170,000	115,000	290,000	621,000	1,410,000	1,910,000
C _{max} (ng/mL)	6130	19,500	36,500	70,700† ⁴	116,000	6330	18,300	37,200	80,200	108,000
T _{max} (h)	4.7	2.0	4.0	3.5† ⁴	4.0	2.7	2.0	2.4	3.2	3.2
	Day 273									
AUC(0-t) (ng*h/mL)	109,000	306,000	534,000	1,170,000† ⁴	1,890,000	108,000† ²	289,000	548,000	1,290,000	1,610,000† ³
C _{max} (ng/mL)	5650	17,600	30,600	64,900† ⁴	100,000	5990† ²	17,900	33,900	74,800	91,000† ³
T _{max} (h)	2.7	2.7	2.0	3.0† ⁴	3.2	3.0† ²	2.0	2.0	3.2	3.3† ³

N = 3 at 0.25 and 1.0 mg/kg/day and N = 5 at 2.0, 4.0, and 6.0 mg/kg/day, except where designated with †^N
Source: Text Table 14 (Page 48) in 4.2.3.2 Study No. 20086030 Amended Final Report 2

Organ weights/Gross pathology

There were no drug-related gross observations or organ weight differences on Days 274 (termination) or 330 (recovery).

Histopathology

Treatment-related histopathology findings at terminal necropsy consisted predominantly of inflammatory cell infiltrates of various organs at all doses, with generally a dose-related incidence and severity. Mononuclear and/or mixed cell interface infiltrates and epithelial vesicular degeneration/erosions/necrosis were prominent in the tongue, cervix, vagina, esophagus, stomach, and skin. Other findings included salivary gland duct degeneration/regeneration, uterine endometrial degeneration, increased cellularity of the thymus, and epithelial vesicular degeneration in the cervix accompanied by increased incidence and severity of squamous metaplasia and epithelial erosions ([Table 39](#)).

In the 3 animals sacrificed prematurely (LD animal 2501 with colitis, MHD and HD animals 5003 and 6503 with skin ulcerations and erosions), histopathology findings included liver fibrosis with biliary duct degeneration and lung edema (5003) and moderate pancreatic acinar degeneration (all 3 animals) or pancreatic duct degeneration/regeneration with acinar atrophy (2501). One MD animal (4003) had pancreatic acinar cell degeneration with fibrosis/fibroplasia, similar to that noted in animals sacrificed prematurely.

After the recovery period, inflammatory cell infiltrates of most organs and the administration sites were considered completely recovered; however, mucosal infiltrates of the esophagus, squamous metaplasia of the cervical mucosa, increased medullary cellularity in the thymus, and

lymphoid follicles or aggregates in the bone marrow remained present although decreased in incidence and/or severity ([Table 40](#)).

Table 39. Microscopic Findings - Early Sacrifice (Bold) and End of Dosing (Amended Report)

Group Dose (mg/kg/day) No. animals examined	Males						Females					
	1	2	3	4	5	6	1	2	3	4	5	6
	0	0.25	1.0	2.0	4.0	6.0	0	0.25	1.0	2.0	4.0	6.0
Pancreas	3	3	3	3	3	3	3	3	3	3	3	2
Acinar cell degeneration with/without fibrosis/fibroplasia	(0) ^a	(0)	(0)	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Minimal ^b	0	0	0	4003 ^c	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	5003	0	0	0	0	0	0	6503
Ductal hyperplasia	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
degeneration/regeneration	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Moderate	0	0	0	0	0	0	0	2501	0	0	0	0
Acinar atrophy	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Moderate	0	0	0	0	0	0	0	2501	0	0	0	0
Spleen												
Increased cellularity, germinal centers, lymphoid follicles	(0)	(0)	(2)	(3)	(2)	(1)	(0)	(0)	(2)	(1)	(1)	(2)
Minimal	0	0	3001 3002	4001 4002	5001	6003	0	0	0	4503	5501	6501
Mild	0	0	0	4003	5003	0	0	0	3501 3502	0	0	6502
Thymus												
Lymphoid follicle formation	(0)	(0)	(1)	(3)	(2)	(2)	(0)	(0)	(1)	(1)	(1)	(2)
Minimal	0	0	3002	4001	0	0	0	0	3502	0	5501	0
Mild	0	0	0	4003	5002 5003	6001 6002	0	0	0	4501	0	0
Moderate	0	0	0	4002	0	0	0	0	0	0	0	6502
Marked	0	0	0	0	0	0	0	0	0	0	0	6501
Increased cellularity of the medulla	(0)	(0)	(1)	(2)	(2)	(2)	(0)	(0)	(1)	(1)	(2)	(3)
Minimal	0	0	0	4003	0	6002	0	0	3501	0	5501 5502	0
Mild	0	0	3002	0	0	0	0	0	0	4501	0	6502 6503
Moderate	0	0	0	4002	5002	6003	0	0	0	0	0	6501
Marked	0	0	0	0	5001	0	0	0	0	0	0	0

Bone Marrow												
Lymphoid aggregates	(1)	(0)	(1)	(0)	(1)	(2)	(0)	(0)	(2)	(1)	(0)	(3)
Minimal	1003	0	3002	0	5003	6002 6003	0	0	3502 3503	4503	0	6501 6502 6503
Lymphoid follicle formation	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(3)
Minimal	0	0	0	0	0	6002	0	0	0	0	0	6501
Mild	0	0	0	0	0	0	0	0	0	0	0	6502 6503
Liver												
Fibrosis/fibroplasia with biliary hyperplasia ductal degeneration/regeneration	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Moderate	0	0	0	0	5003	0	0	0	0	0	0	0
Lung												
Pulmonary edema	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Marked	0	0	0	0	5003	0	0	0	0	0	0	0
Salivary Gland												
Duct hyperplasia degeneration/regeneration	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Moderate	0	0	0	0	0	0	0	0	0	0	0	6503
Uterus												
Endometrial degeneration	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
Mild	NA	NA	NA	NA	NA	NA	0	0	3501	0	0	0
Marked	NA	NA	NA	NA	NA	NA	0	0	0	0	0	6503

NA = finding not applicable to the sex of the animals. **Bold** indicates an early euthanasia animal.

^a Numbers in parentheses represent the number of animals with the finding.

^b Severity grades for which there were no findings were omitted from the table.

^c Animal numbers as they appear in the Appendices.

Source: Text Table 5 (Pages 19-20) in 4.2.3.2 Study No. 20086030 Amended Final Pathology Report #2

Table 40. Microscopic Findings - End of Recovery Period (Amended Pathology Report)

	Group	Males				Females			
		1	4	5	6	1	4	5	6
	Dose (mg/kg/day)	0	2.0	4.0	6.0	0	2.0	4.0	6.0
	No. animals examined	2	2	2	2	2	2	2	2
Cervix									
Epithelial squamous metaplasia		(0) ^a	(0)	(0)	(0)	(0)	(1)	(2)	(1)
Minimal ^b		NA	NA	NA	NA	0	0	5504 ^c	6505
Mild		NA	NA	NA	NA	0	4504	0	0
Marked		NA	NA	NA	NA	0	0	5505	0
Esophagus									
Submucosa/mucosal mononuclear cell infiltrates		(0)	(1)	(2)	(1)	(1)	(1)	(1)	(2)
Minimal		0	4005	5004 5005	6005	1505	0	5505	6505
Mild		0	0	0	0	0	4504	0	6504
Thymus									
Lymphoid follicle formation, resolving		(0)	(1)	(1)	(1)	(0)	(0)	(2)	(0)
Minimal		0	0	5004	0	0	0	5504 5505	0
Mild		0	4004	0	6004	0	0	0	0
Increased cellularity of the medulla		(0)	(1)	(0)	(1)	(0)	(0)	(1)	(1)
Minimal		0	4004	0	6004	0	0	5504	6505
Bone Marrow									
Lymphoid aggregates		(0)	(0)	(1)	(0)	(0)	(1)	(1)	(1)
Minimal		0	0	5005	0	0	4504	5505	6505
Lymphoid follicle formation, resolving		(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
Minimal		0	0	5005	0	0	0	0	0

NA = finding not applicable to the sex of the animals.

^a Numbers in parentheses represent the number of animals with the finding.

^b Severity grades for which there were no findings were omitted from the table.

^c Animal numbers as they appear in the Appendices.

Source: Text Table 6 (Page 21) in 4.2.3.2 Study No. 20086030 Amended Final Pathology Report #2

13.2.2. Reproductive and Developmental Toxicity

Table 41. Study Title: RA101495 13-Week Subcutaneous Administration Male Fertility Study in the Cynomolgus Monkey With an 8-Week Recovery Phase

Description	Parameter
Study no.:	8366459
Study report location:	4.2.3.5.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 July 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, batch #, purity:	RA101495, QP010208, 97.8%

Source: Study report

Table 42. Study Methods

Methods	Parameters
Doses:	0 (vehicle), 1.0, 2.0, or 4.0 mg/kg/day
Frequency of dosing:	QD
Route of administration:	SC
Dose volume:	0.2 mL/kg
Formulation/Vehicle:	(b) (4) sodium phosphate pH 7.0
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	4 males/group main, 2 males/group recovery
Age:	4 to 9 years
Weight:	4.2 to 8.5 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that impacted study quality or integrity

Source: Study Report

Endpoints consisted of mortality, clinical observations, BW, complement activity (ex vivo pharmacodynamic assay at 1, 2, 4, 6, and 24 hours on day 1, week 13, and weeks 4 and 8 of recovery), testicular evaluation (ultrasound during weeks 1, 7, and 13 of the dosing period and the last week of the recovery period), clinical pathology (hematology and coagulation, clinical chemistry, and urinalysis), immunophenotyping, macroscopic and microscopic findings, organ weights, analysis of spermatogenic stages, and immunohistochemistry were evaluated.

The HD was based on previous studies in cynomolgus monkeys in which hepatobiliary toxicity (cholestasis) was observed. The LD was anticipated to result in approximately 1.5X clinical therapeutic levels. All doses were expected to result in complete inhibition of complement activity at the C5 level.

Table 43. Study Design

Group Number	Group Description	Dose Level (mg/kg)	Dose Volume ^a (mL/kg)	Animals/Group	Necropsy after ...	
				Male	13 Weeks	21 Weeks
1	Control	0	0.2	6	4	2
2	Low	1.0	0.2	6	4	2
3	Intermediate	2.0	0.2	6	4	2
4	High	4.0	0.2	6	4	2

^a Based on most recent individual body weight

Source: Text Table 3.1.5 (Page 19) in 4.2.3.5.1 Study No. 8366459 Final Report

Observations and Results

Mortality

There were no unscheduled deaths.

Clinical Signs

There were no drug-related clinical observations.

Body Weights

There were no drug-related differences in BW or BW change.

Food Consumption

There was no effect on food consumption.

Complement Activity

Complement-dependent hemolysis was maintained below approximately 5% for 5 of the 6 LD animals and for all MD and HD animals throughout the 13-week dosing period. Little to no inhibition of hemolysis remained at the end of the recovery period.

Testicular size

There were no clearly drug-related differences in testicular parameters. Over the course of the treatment period, testicular volume increased in C and MD males and decreased in LD and HD males ([Table 44](#)). One HD male (P0303) showed a permanent decrease in testicular size during the dosing period and reduced testicular weight at necropsy.

Table 44. Testicular Data

Test Item		(dosage)	1M	2M	3M	4M
RA101495 sodium salt		mg/kg/day	0	1	2	4
		Phase Day	PRED 1			
		Testicular Volume (mL)				
Group/ Sex		Testis, R	Testis, L	Testes		
1/M	Mean	13.50	13.70	27.20		
	SD	6.831	6.711	13.535		
	N	6	6	6		
2/M	Mean	16.58	17.16	33.74		
	SD	8.771	8.915	17.627		
	N	6	6	6		
3/M	Mean	14.55	15.23	29.78		
	SD	4.425	3.552	7.900		
	N	6	6	6		
4/M	Mean	17.83	17.63	35.46		
	SD	6.854	7.219	14.065		
	N	6	6	6		
Statistics		A	A	A		
A = ANOVA and Dunnett's						
DSNG 87						
Testicular Volume (mL)						
Testis, R		Testis, L	Testes			
17.47		17.68	35.14			
6.633		6.823	13.418			
6		6	6			
15.39		15.36	30.74			
5.872		6.438	12.140			
6		6	6			
18.71		17.90	36.61			
4.073		2.435	6.360			
6		6	6			
15.22		15.24	30.46			
6.229		5.303	11.499			
6		6	6			
A		A	A			

Source: Table 9.5 (Pages 53-55) in 4.2.3.5.1 Study No. 8366459 Final Report

Clinical Pathology

There were no drug-related effects on hematology, coagulation, clinical chemistry, or urinalysis parameters.

Immunophenotyping

There were no clearly drug-related effects on immunophenotyping data.

Terminal sacrifice**Organ weights**

There were no clearly drug-related effects on group mean organ weights; however, the testis weight of 1 HD male (P0303) was notably decreased ([Table 45](#)).

Table 45. Organ Weights – Terminal Sacrifice

Table Individual Organ Weight and Organ Weight Ratios Terminal Sacrifice								
Test Item		(dosage)	1M	2M	3M	4M		
RA101495 sodium salt		mg/kg	0	1	2	4		
Group/ Sex	Animal Number	Terminal Body Weight (g)	Spleen			Testis		
			Unadjusted (g)	Body Weight (%)	Brain Weight (%)	Unadjusted (g)	Body Weight (%)	Brain Weight (%)
1/M	P0003	7235	5.574	0.0770	8.7869	51.681	0.7143	81.4708
	P0004	8055	8.524	0.1058	13.1934	67.289	0.8354	104.1496
	P0005	6540	4.373	0.0669	5.4304	34.079	0.5211	42.3194
	P0006	7725	4.910	0.0636	6.9210	32.171	0.4165	45.3477
	Mean	7389	5.845	0.0783	8.5830	46.305	0.6218	68.3219
	SD	658.5	1.8522	0.01921	3.36642	16.5174	0.18840	29.77954
	N	4	4	4	4	4	4	4
Group/ Sex	Animal Number	Terminal Body Weight (g)	Spleen			Testis		
			Unadjusted (g)	Body Weight (%)	Brain Weight (%)	Unadjusted (g)	Body Weight (%)	Brain Weight (%)
4/M	P0303	6070	5.874	0.0968	8.4158	20.116	0.3314	28.8207
	P0304	7500	9.982	0.1331	13.2957	34.350	0.4580	45.7530
	P0305	6955	10.580	0.1521	15.5155	68.198	0.9806	100.0117
	P0306	6870	9.978	0.1452	15.0106	50.040	0.7284	75.2787
	Mean	6849	9.104	0.1318	13.0594	43.176	0.6246	62.4660
	SD	589.4	2.1715	0.02465	3.23821	20.6791	0.28937	31.54455
	N	4	4	4	4	4	4	4

Source: Table 8.1 (Pages 69-72) in 4.2.3.5.1 Study No. 8366459 Anatomic Pathology Report

Macroscopic

There were no notable macroscopic findings.

Microscopic

Testicular germ cell depletion/degeneration (minimal to slight, unilateral or bilateral) was observed in 2 LD (P0104, P0106), 3 MD (P0203, P0204, and P0206), and 2 HD animals (P0303, P0304). Testicular fibrosis was also observed in animal P0304 ([Table 46](#)). According to the pathology report: “Degeneration/depletion of germ cells in the testicular tubules were characterized by various combinations of tubular dilatation, tubular vacuolation, reduced height of germinal epithelium, reduced spermatogenesis stages, and tubuli with sertoli cells only.” It was reported that “spermatogenesis was complete, and all spermatogenic stages were present in the testes of all animals.”

Table 46. Microscopic Observations - Terminal Sacrifice

Test Item	(dosage)	1M	2M	3M	4M
RA101495 sodium salt	mg/kg/day	0	1	2	4
Tissue/ Observation	Group/Sex: Number of Animals:	1/M 4	2/M 4	3/M 4	4/M 4
Epididymis	Number Examined:	4	4	4	4
	Unremarkable:	4	2	4	4
Infiltrate, mononuclear cells		0	2	0	0
Prostate	Number Examined:	4	4	4	4
	Unremarkable:	1	0	3	1
Infiltrate, mononuclear cells		3	4	1	3
Seminal Vesicle	Number Examined:	4	4	4	4
	Unremarkable:	3	4	4	4
Ectasia, duct		1	0	0	0
Testis	Number Examined:	4	4	4	4
	Unremarkable:	4	2	1	2
Depletion/degeneration, germ cell		0	2	3	2
Fibrosis		0	0	0	1
Thymus	Number Examined:	4	4	4	4
	Unremarkable:	0	0	0	0
Involution		4	4	4	4

Source: Table 7.5 (Page 42) in 4.2.3.5.1 Study No. 8366459 Anatomic Pathology Report

Recovery sacrifice**Organ weights**

Testis weights were decreased at all doses compared to C, although not in a dose-related manner ([Table 47](#)). In addition, 1 C male (P0001) appeared to be an outlier.

Table 47. Organ Weights – Recovery Sacrifice

Individual Organ Weight and Organ Weight Ratios

Recovery Sacrifice

Test Item		(dosage)	1M	2M	3M	4M			
RA101495 sodium salt		mg/kg	0	1	2	4			
Group/ Sex	Animal Number	Terminal Body Weight (g)	Spleen			Testis			
			Unadjusted (g)	Body Weight (%)	Brain Weight (%)	Unadjusted (g)	Body Weight (%)	Brain Weight (%)	
1/M	P0001	6950	6.523	0.0939	9.6110	70.578	1.0155	103.9900	
	P0002	4855	3.653	0.0752	5.0624	37.882	0.7803	52.4972	
	Mean	5903	5.088	0.0845	7.3367	54.230	0.8979	78.2436	
	SD	1481.4	2.0294	0.01316	3.21639	23.1196	0.16634	36.41087	
	N	2	2	2	2	2	2	2	
2/M	P0101	5470	5.129	0.0938	7.2850	29.523	0.5397	41.9331	
	P0102	4590	5.434	0.1184	8.2219	25.358	0.5525	38.3677	
	Mean	5030	5.282	0.1061	7.7534	27.441	0.5461	40.1504	
	SD	622.3	0.2157	0.01741	0.66247	2.9451	0.00901	2.52110	
	N	2	2	2	2	2	2	2	
3/M	P0201	6510	7.466	0.1147	9.3867	33.639	0.5167	42.2930	
	P0202	5350	6.809	0.1273	9.5748	23.713	0.4432	33.3451	
	Mean	5930	7.138	0.1210	9.4807	28.676	0.4800	37.8190	
	SD	820.2	0.4646	0.00890	0.13298	7.0187	0.05197	6.32715	
	N	2	2	2	2	2	2	2	
4/M	P0301	5580	10.044	0.1800	15.8914	39.567	0.7091	62.6021	
	P0302	6585	5.054	0.0768	8.2613	29.167	0.4429	47.6764	
	Mean	6083	7.549	0.1284	12.0763	34.367	0.5760	55.1392	
	SD	710.6	3.5285	0.07301	5.39531	7.3539	0.18820	10.55402	
	N	2	2	2	2	2	2	2	

Source: Table 8.2 (Pages 87-88) in 4.2.3.5.1 Study No. 8366459 Anatomic Pathology Report

Macroscopic

There were no notable macroscopic findings.

Microscopic

Testicular germ cell depletion/degeneration was observed in both LD, 1 MD, and both HD animals at terminal sacrifice (Table 49). Fibrosis was also observed in 1 LD animal.

Table 48. Microscopic Observations - Recovery Sacrifice

Test Item		(dosage)	1M	2M	3M	4M
RA101495 sodium salt		mg/kg/day	0	1	2	4
Tissue/ Observation	Group/Sex:		1/M	2/M	3/M	4/M
	Number of Animals:		2	2	2	2
Testis	Number Examined:		2	2	2	2
	Unremarkable:		2	0	1	0
	Depletion/degeneration, germ cell		0	2	1	2
	Fibrosis		0	1	0	0

Source: Table 7.6 (Page 43) in 4.2.3.5.1 Study No. 8366459 Anatomic Pathology Report

Immunohistochemistry

When thymus tissue was examined for immune composition by immunohistochemistry [mC]) using mC-specific for CD3, CD4, CD8, CD20, and CD45, there was a minimal overall decrease in the number/distribution of CD3, CD4, and CD8 positive cells in HD animals, at both the terminal and recovery sacrifices. There were no clear effects on thymic CD20+ve, or CD45+ve cells at any dose. An increase in the incidence and severity of thymic involution/atrophy/lymphoid depletion was noted in HD animals.

Toxicokinetics

Exposure increased with increasing dose in an approximately dose-proportional manner ([Table 49](#)). Absorption of zilucoplan was prolonged, with T_{max} values observed between 1 and 6 hours postdose. Approximately 2-fold accumulation was observed over the 13-week dosing period. T_{1/2} could only be calculated in recovery animals and ranged from approximately 79 hours to 108 hours and decreased with increasing dose.

Table 49. TK parameters for RA101495 in Cynomolgus Monkeys

Group	Dose (mg/kg)	Variable	N	Day 1			Day 91		
				Mean	SD	CV%	Mean	SD	CV%
2	1.0	AUC ₀₋₂₄ (h*ng/mL)	6	227000	23900	10.5	488000	109000	22.4
		AUC ₀₋₂₄ /D	6	227000	23900	10.5	488000	109000	22.4
		C _{max} (ng/mL)	6	12100	880	7.31	25300	4910	19.4
		C _{max} /D	6	12100	880	7.31	25300	4910	19.4
		T _{max} (h)	6	3.67	0.816	22.3	2.83	1.33	46.9
		T _{1/2} ^a (h)	1	NA	NA	NA	108	NA	NA
		AUC ₀₋₂₄ (h*ng/mL)	6	445000	23900	5.37	998000	90900	9.11
3	2.0	AUC ₀₋₂₄ /D	6	223000	12000	5.37	499000	45500	9.11
		C _{max} (ng/mL)	6	25300	2450	9.7	52900	3970	7.5
		C _{max} /D	6	12600	1230	9.7	26500	1980	7.5
		T _{max} (h)	6	3.00	1.10	36.5	3.00	1.10	36.5
		T _{1/2} ^a (h)	2	NA	NA	NA	94.4	NA	NA
		AUC ₀₋₂₄ (h*ng/mL)	6	843000	64800	7.69	1990000	283000	14.2
		AUC ₀₋₂₄ /D	6	211000	16200	7.69	497000	70800	14.2
4	4.0	C _{max} (ng/mL)	6	46200	2860	6.18	103000	11300	11
		C _{max} /D	6	11600	714	6.18	25600	2830	11
		T _{max} (h)	6	4.67	1.03	22.1	5.00	1.10	21.9
		T _{1/2} ^a (h)	1	NA	NA	NA	78.9	NA	NA

Note – Units for AUC₀₋₂₄/D and C_{max}/D are (h*ng/mL)/(mg/kg) and (ng/mL)/(mg/kg), respectively

NA = Not applicable

a = Calculated from monkeys assigned to the recovery phase only.

Source: Text Table 4.2 (Page 31) in 4.2.3.5.1 Study No. 8366459 Final Report

Table 50. Study Title: RA101495 Enhanced Subcutaneous Study for Effects on Embryo-Fetal and Pre- and Postnatal Development in Cynomolgus Monkeys With Three Months Lactation/Maturation Phase

Description	Parameter
Study no.:	8340294
Study report location:	4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	27 September 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RA101495, 7002753, 93.3% and QP010208, 97.8%

Source: Study Report

Table 51. Study Methods

Methods	Parameter
Doses:	0 (vehicle), 1, 2, or 4 mg/kg
Frequency of dosing:	QD
Route of administration:	subcutaneous (SC)
Dose volume:	0.2 mL/kg
Formulation/Vehicle:	(b) (4) sodium phosphate, pH 7.0
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4 females/group EFD, 16/group PPND
Age:	approx. 4 years
Weight:	at least 2.5 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that impacted study quality or integrity

Source: Study Report

Zilucoplan was administered to pregnant cynomolgus monkeys from GDs 20 to 100 with C-section afterwards or from GD 20 to delivery (approximately GD 160). Embryofetal development was assessed at GD 100 in 4/group. Pregnancy loss and offspring survival, growth, and postnatal development were assessed up to PND 91±1 in 16/group ([Table 52](#)).

Table 52. Experimental Design

Group Number	Group Description	Color Code	Number of Pregnant Females with Cesarean Section on Day 100 ± 1 p.c.	Number of Pregnant Females with Delivery	Dose Level (mg/kg)	Dose Volume* (mL/kg)
1	Control	White	4	16	0	0.2
2	Low	Blue	4	16	1.0	0.2
3	Mid	Green	4	16	2.0	0.2
4	High	Red	4	16	4.0	0.2

* Based on most recent individual body weight

Source: Table 3.1.7 (Page 26) in 4.2.3.5.3 Study No. 8340294 Final Report

Results

EFD Phase

Maternal evaluations

Mortality

There were no unscheduled maternal deaths.

Clinical Signs

There were no drug-related maternal clinical observations.

Microbiological Analysis

Microbiological analysis of vaginal swabs during gestation did not indicate a drug-related effect. Microbiological infections were evenly distributed among all groups, including C.

Body Weights

There were no drug-related differences in maternal BWs or BW change.

Food Consumption

There was no effect on maternal food consumption.

Clinical Pathology

There were no effects on clinical chemistry parameters.

Bioactivity

CH50 bioactivity was decreased compared to C in all animals from all dose groups on GDs 58 (SS) and 90 (NS) ([Table 53](#)).

Table 53. Maternal Complement Factor – EFD Phase

		Plasma Complement - MS :MS- Complement CH50(CH50.)-(U/mL)		
		Females		
Group #		Gestation Day: 20 Session: S4	Day: 58 Session: S4	Day: 90 Session: S4
Control	(n)	4	4	4
	Means	30.77	35.82	20.11
	Sdevs	0.770	5.682	3.656
2	(n)	4	4	4
	Means	41.89	12.53#H	14.38
	Sdevs	12.445	1.230	2.315
3	(n)	3@	3@	3
	Means	56.08*H	12.22#H	13.58
	Sdevs	14.160	4.535	0.485
4	(n)	4	4	4
	Means	32.31	13.86#H	16.01
	Sdevs	10.446	3.806	6.496

*H = Dunnett Exact Homogeneous Test Significant: 0.05 level

#H = Dunnett Exact Homogeneous Test Significant: 0.001 level

@= Number examined reduced due to excluded data

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

Source: Table 9.6 (Page 101) in 4.2.3.5.3 Study No. 8340294 Final Report

Organ Weights

There were no drug-related differences maternal organ weights.

Macroscopic Pathology

There were no drug-related macroscopic findings.

Cesarean Section Data

There were no apparent drug-related effects on pregnancy outcome ([Table 54](#)). One MD female (70486F) had an abortion on GD 64.

Table 54. Pregnancy Outcome - EFD Phase

Test Item	(dosage)	1	2	3	4
RA101495	mg/kg from GD 20	0	1	2	4
Group/Sex:		1/F	2/F	3/F	4/F
Number of Pregnant Females:		4	4	4	4
Number of females with abortion		0	0	1	0
Number of females with live fetus(es)		4	4	3	4
Number of fetuses examined		4	4	3	4
Number of live male fetus(es)		1	2	2	3
Number of live female fetus(es)		3	2	1	1

Source: Table 9.1 (Page 89) in 4.2.3.5.3 Study No. 8340294 Final Report

Fetal Evaluations

Fetal weights, body measurements, and organ weights

There were no clearly treatment-related effects.

Fetal external, visceral, and skeletal development

Fetal external, visceral, and skeletal examinations did not indicate any clearly drug-related findings ([Table 55](#)). Variations were evenly distributed across all groups. External malformations of kinked tail in 1 LD (70525-1) and 2 HD fetuses (70305-1 and 70707-1) were due to skeletal misalignment of vertebrae 53 to 54 (70525-1) and of the zygoistyle (70305-1 and 70707-1). These were considered background findings and unrelated to treatment.

Table 55. Fetal Findings at Cesarean Section.

Test Item (dosage)	1	2	3	4
RA101495 mg/kg from GD 20	0	1	2	4
Group:	1	2	3	4
Number of fetuses examined:	4	4	3	4
Malformations	Number of animals affected			
Total number of fetuses with				
- no external abnormalities	2	2	0	2
- no visceral abnormalities	4	3	3	2
- no skeletal abnormalities	0	0	0	0
Total number of fetuses with malformations	0	1	0	2
<u>External malformations</u>				
Number of fetuses with malformations	0	1	0	2
<u>Tail</u>				
kinked, tip of tail	0	1	0	2
<u>Visceral malformations</u>				
Number of fetuses with malformations	0	0	0	0
<u>Skeletal Findings</u>				
Number of fetuses with malformations	0	1	0	2
<u>Vertebral column</u>				
Vertebra, 53, 54, misaligned	0	1	0	0
Zygostyle, misaligned	0	0	0	2

Source: Table 9.13 (Pages 142-143) in 4.2.3.5.3 Study No. 8340294 Final Report

PPND Phase

Maternal Evaluations

Mortality

There were no unscheduled maternal deaths.

Clinical Signs

There were no drug-related maternal clinical observations.

Microbiological Analysis

There were no drug-related microbiological findings in vaginal swabs.

Body Weights

There were no drug-related differences in maternal BW or BW change.

Food Consumption

There was no effect on maternal food consumption.

Clinical Pathology

There were no effects on clinical chemistry parameters.

Bioactivity

CH50 bioactivity was decreased compared to C in all animals from all dose groups throughout the gestational dosing period ([Table 56](#)). Activity was similar among all groups during the lactation period.

Table 56. Maternal Complement Factor – ePPND Phase

		Plasma Complement CH50 (U/mL)				
		Females				
Group #		Gestation Day: 20 Session: S4	Day: 58 Session: S4	Day: 90 Session: S4	Day: 142 Session: S4	Day: 158 Session: U1
Control	(n)	15@	14	15	15	0
	Means	39.34	34.33	31.87	37.35	-
	Sdevs	8.890	10.382	6.020	6.765	-
2	(n)	13@	13@	13@	13	0
	Means	43.96	19.51#r	19.73#H	19.29#r	-
	Sdevs	13.975	4.376	3.721	4.404	-
3	(n)	13@	13	13	12	1
	Means	38.15	15.40#r	18.15#H	16.08#r	23.89
	Sdevs	7.473	4.428	5.695	4.761	-
4	(n)	11@	11@	11@	10	0
	Means	44.49	17.36#r	17.18#H	16.83#r	-
	Sdevs	10.806	5.447	3.381	3.261	-

#r = Wilcoxon rank Sum Test Significant at 0.001 level.

#H = Dunnett Exact Homogeneous Test Significant: 0.001 level

@ = Number examined reduced due to excluded data

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

Source: Table 11.4 (Page 343) in 4.2.3.5.3 Study No. 8340294 Final Report

Pregnancy Outcome

Prenatal loss, detected by ultrasound, was increased compared to C in all treatment groups: 1/16 (6.25%) C, 5/16 LD (31.25%), 4/16 (25.0%), and 5/16 (31.25%) HD dams experienced pregnancy loss prior to parturition, not counting stillbirth ([Table 57](#) and [Table 58](#)). (Fetal loss prior to GD 140 in cynomolgus monkeys is typically defined as abortion, that after GD 140 as stillbirth.) Embryofetal deaths occurred throughout the dosing period in drug-treated groups.

Stillbirths (infants died prior or during birth and their lungs were not inflated; stillbirth and infant death considered postnatal losses in study report) were observed in 3/15 (20.0%) C, 1/11 (9.1%) LD, 2/12 (16.7%) MD, and 1/11 (9.1%) HD pregnancies (while all C stillbirths occurred after GD 140, 1 MD and 1 HD stillbirth occurred earlier). The number of live born infants was 12, 10, 10, and 10 in C, LD, MD, and HD groups, respectively.

Table 57. Pregnancy Outcome – ePPND Phase

Test Item	(dosage)	1F	2F	3F	4F
RA101495	mg/kg from GD 20	0	1	2	4
Group/Sex:		1/F	2/F	3/F	4/F
Number of Pregnant Females:		16	16	16	16
Total number of females with abortion		1	3	3	5
Percentage of pre-natal loss		6.3	18.8	18.8	31.3
Total number of unscheduled cesarean section due to intra-uterine death		-	2	1	-
Total number of stillbirths		3	1	2	1
Total number of infants found dead		1	1	1	-
Total number of infants sacrificed moribund		2	-	-	2
Duration of Gestation (days)		Mean	160.9	161.2	158.5
(normal delivery, stillbirth, unscheduled cesarean section)		SD	9	9	14
		N	15	13	13

Source: Table 11.1 (Page 336) in 4.2.3.5.3 Study No. 8340294 Final Report

Table 58. Pregnancy Outcome and Infant Loss

Animals	Early Pregnancy Loss	Mid Pregnancy Loss	Late Pregnancy Loss	Stillbirths ^a , including Death During Birth	Total Pregnancy Loss	Infant Loss	Total Infant Loss
Group/ Dose	N	(GD 20 to 50)	(GD 51 to 100)	(GD 101 to 175)	(GD 20 to 175)	Maturation Days	
Group 1 (0 mg/kg)	16	71276 (GD 30) 6.25%	-	-	71305 (GD153); 70663 (GD154); 70405 (GD175) 18.75%	4 70666-1 (MD2); 71207-1 (MD2); 71236-1 (MD9) 25%	3/12
Group 2 (1.0 mg/kg)	16	-	71237 (GD72) 6.25%	70982 (GD113); 70850 (GD115); 71173 (GD142); 71179 (GD166); 25%	6 70673 (GD154) 6.25%	6 70648-1 (MD67) 10%	1/10
Group 3 (2.0 mg/kg)	16	71249 (GD30); 71289 (GD29) 12.5%	71238 (GD35) 6.25%	70985 (GD158) 6.25%	6 71036 (GD123); 71259 (GD143) 12.5%	6 71230-1 (MD1) 10%	1/10
Group 4 (4.0 mg/kg)	16	71283 (GD30); 71239 (GD31); 12.5%	70991 (GD55) 6.25%	71310 (GD101); 70657 (GD114) 12.5%	6 71181 (GD132) 6.25%	6 71006-1 (MD9); 71254-1 (MD16) 20%	2/10

GD = Gestation Day; MD = Maturation Day.

^a = Stillbirth is defined as a born infant with a lung that has not been inflated with air (determined by a lung flotation test).

Source: Text Table 4.6 (Page 60) in 4.2.3.5.3 Study No. 8340294 Final Report

Offspring Data

Survival

There was no drug-related effect on infant survival ([Table 59](#)).

Table 59. Survival Indices

Parameter	0.0 mg/kg	1.0 mg/kg	2.0 mg/kg	4.0 mg/kg
Live born	12	10	10	10
Alive on				
LD 1	12	10	9	10
LD 7	10	10	9	10
LD 90 ±1 day	9	9	9	8
Survival index (%) LD 90	75	90	90	80

LD = Lactation day.

Source: Text Table 4.9 (Page 66) in 4.2.3.5.3 Study No. 8340294 Final Report

Clinical Observations

There were no drug-related clinical observations.

Body Weights

BW gain was decreased (SS) in HD males during the first week ([Table 60](#)); however, final BWs were similar among groups in males, and no BW effect was seen in females.

Table 60. Infant Body Weight Change

Test Item (dosage)		1F 2F 3F 4F					
RA101495 mg/kg from GD 20		0 1 2 4					
		Data Presented in "g" Interval X through X					
Group/ Sex	Phase	MAT					
	Day	1 - 7	7 - 14	14 - 21	21 - 28	28 - 56	56 - 84
1/M	Mean	19	25	28	15	116	111
	SD	11.7	8.7	8.3	5.9	10.0	23.1
	N	4	4	4	4	4	4
2/M	Mean	21	30	27	16	131	122
	SD	9.2	5.6	7.8	6.9	29.5	18.4
	N	5	5	5	5	5	4
3/M	Mean	11	16	24	20	103	118
	SD	11.6	10.4	21.3	23.2	34.5	33.0
	N	7	7	7	7	7	7
4/M	Mean	-23**	17	14	7	101	130
	SD	27.4	13.3	10.4	9.5	32.7	13.0
	N	4	3	3	3	3	3
Statistics		A	A	A	A	A	A

Source: Table 11.17 (Page 451) in 4.2.3.5.3 Study No. 8340294 Final Report

External Observations

Abnormalities noted in 2 LD infants (shortened thumbs on both hands) were considered incidental because they were not dose dependent and were not detected in the radiographic assessment.

Morphological Measurements

There were no apparent drug-related differences among groups.

Neurobehavioral Assessments

There were no drug-related effects on scores in a neurobehavioral test battery performed on PNDs 1 and 7. Grip strength was not different among groups.

Skeletal Development

Radiographic evaluations of offspring on PND 35 did not indicate drug-related skeletal changes.

Clinical Pathology

There were no clear effects on hematological or clinical chemistry parameters.

Immunophenotyping

There were no apparent drug-related differences among groups.

Bioactivity

No drug-related effects on CH50 bioactivity were detected on PND 35 or 90.

Organ Weights

There were no apparent drug-related differences among groups.

Macroscopic Observations

There were no unusual findings at the terminal necropsy. Among the 7 offspring that died during the postnatal observation period, a heart malformation was found in 1 HD female that was sacrificed moribund on PND 16 (71254F-1). Although heart malformations are rare (12 cases in 947 control fetuses/infants in lab historical data), this was not considered drug-related in the study report due to the isolated nature of the finding. However, because it occurred at the HD and not all offspring that died early were examined, it should be considered of uncertain relation to treatment.

Toxicokinetics

TK data in pregnant females on at the beginning and near the end of the dosing period are shown in [Table 61](#).

Table 61. TK Parameters for RA101495 in Pregnant Monkeys on GDs 20 and 142

Generation	Matrix	GD	Group	Dose (mg/kg)	Variable	N	Mean	SD	CV%
Maternal	Plasma	20	2	1.0	AUC _(0-t) /D	20	230,000	23,900	10.4
					AUC _(0-t) (ng*h/mL)	20	230,000	23,900	10.4
					C _{max} (ng/mL)	20	12,800	1320	10.3
					C _{max} /D	20	12,800	1320	10.3
					T _{max} (h)	20	3.35	1.46	43.6
Maternal	Plasma	20	3	2.0	AUC _(0-t) /D	20	205,000	25,000	12.2
					AUC _(0-t) (ng*h/mL)	20	411,000	50,000	12.2
					C _{max} (ng/mL)	20	23,900	3010	12.6
					C _{max} /D	20	12,000	1500	12.6
					T _{max} (h)	20	3.75	1.33	35.5
Maternal	Plasma	20	4	4.0	AUC _(0-t) /D	20	194,000	25,700	13.2
					AUC _(0-t) (ng*h/mL)	20	776,000	103,000	13.2
					C _{max} (ng/mL)	20	44,900	5430	12.1
					C _{max} /D	20	11,200	1360	12.1
					T _{max} (h)	20	4.20	0.616	14.7
Generation	Matrix	GD	Group	Dose (mg/kg)	Variable	N	Mean	SD	CV%
Maternal	Plasma	142	2	1.0	AUC _(0-t) /D	13	308,000	37,000	12.0
					AUC _(0-t) (ng*h/mL)	13	308,000	37,000	12.0
					C _{max} (ng/mL)	13	18,800	2360	12.5
					C _{max} /D	13	18,800	2360	12.5
					T _{max} (h)	13	3.54	1.13	31.8
Maternal	Plasma	142	3	2.0	AUC _(0-t) /D	12	294,000	27,700	9.44
					AUC _(0-t) (ng*h/mL)	12	588,000	55,500	9.44
					C _{max} (ng/mL)	12	37,000	3940	10.7
					C _{max} /D	12	18,500	1970	10.7
					T _{max} (h)	12	3.92	1.08	27.7
Maternal	Plasma	142	4	4.0	AUC _(0-t) /D	10	298,000	46,500	15.6
					AUC _(0-t) (ng*h/mL)	10	1,190,000	186,000	15.6
					C _{max} (ng/mL)	10	72,900	8620	11.8
					C _{max} /D	10	18,200	2160	11.8
					T _{max} (h)	10	4.40	0.843	19.2

Note: Units for dose-normalized AUC_(0-t)/D and C_{max}/D are (ng*h/mL)/(mg/kg) and (ng/mL)/(mg/kg), respectively.

Source: Text Table 4.4 (Pages 48-51) in 4.2.3.5.3 Study No. 8340294 Final Report

13.2.3. Genetic Toxicology

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Table 62. Study Title: Zilucoplan [RA101495]: Micronucleus Test in Bone Marrow Cells of the Sprague-Dawley Rat

Description	Parameter
Study no:	20334416
Study report location:	4 2 3 3 2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 Oct 2021
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	RA101495, 23-21 -0016-01, 97%

Source: Study Report

Methods and Results

In the dose range-finding study (250, 500, or 2000 mg/kg), the MTD was estimated to be 500 mg/kg based on clinical signs at the HD (male: rough coat and hunched posture, male and female: large lesion in the belly which was dark stained and hairless). In the micronucleus assay, SD rats (5 males/dose) were administered zilucoplan twice (at a 24 h interval) by SC injection and euthanatized 48 hours after the first dosing for extraction of the bone marrow. RA101495 did not induce a significant increase in micronuclei in bone ([Table 63](#)).

Table 63. Micronucleated PCEs After RA101495 Administration to SD Rats

Group	Treatment	Dose (mg/kg body weight)	Number of micronucleated polychromatic erythrocytes (mean ± S.D.) ⁽³⁾			Ratio polychromatic/normochromatic erythrocytes (mean ± S.D.) ⁽⁴⁾		
1	Vehicle Control ⁽¹⁾	0	2.4	±	2.7	0.80	±	0.23
2	Zilucoplan ⁽¹⁾	125	3.4	±	2.5	0.79	±	0.11
3	Zilucoplan ⁽¹⁾	250	1.4	±	1.1	0.82	±	0.09
4	Zilucoplan ⁽¹⁾	500	3.2	±	2.9	0.79	±	0.19
5	CP (subcutaneous) ⁽²⁾	19	9.3	±	7.1 ⁽⁵⁾	0.40	±	0.12 ⁽⁵⁾
6	CP (oral) ⁽²⁾	19	31.3	±	0.6 ⁽⁵⁾	0.36	±	0.03 ⁽⁵⁾

Vehicle control = 50 mM Sodium Phosphate

CP = Cyclophosphamide.

(1) Five animals per treatment group.

(2) Three animals per treatment group.

(3) At least 4000 polychromatic erythrocytes were evaluated with a maximum deviation of 5%.

(4) The ratio was determined from at least the first 500 erythrocytes counted.

(5) Significantly different from corresponding control group (Students t test, P < 0.001).

Source: Table 6 (Page 33) in 4.2.3.3.2 Study No. 20334416 Final Report

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

Zilucoplan is highly bound to plasma protein (>99%).

The binding of zilucoplan and its metabolites were determined by equilibrium dialysis (Study #Trial [TR]-0122) and/or equilibrium shift assay (Study # 355-1). For zilucoplan, the observed % unbound fraction as presented below ([Table 64](#)) was independent of concentration within the concentration range tested. The plasma protein binding for zilucoplan, RA102758, and RA103488 was >99%.

Table 64. In Vitro Assessment of Plasma Protein Binding for Zilucoplan, RA102758, and RA103488

Study	Compound	Species	Concentrations tested (μM)	% Unbound
TR-0122	Zilucoplan	Rat	5, 10, and 100	<0.1
		Monkey	5, 10, and 100	<0.1
		Human	10 and 100	<0.1
355-1 ^a	Zilucoplan	Rat	1	0.10
		Monkey	1	0.08
		Human	1	0.17
	RA102758	Rat	1	0.11
		Monkey	1	0.24
		Human	1	0.14
	RA103488	Rat	1	0.45
		Monkey	1	0.91
		Human	1	0.66

^a For Study 355-1, the values of % Unbound are reported as the mean values of the duplicates.

Source: Table 4-1 (Pg 18 of 36) from Module 2.6.4 Pharmacokinetics Written Summary

14.1.2. Blood-to-Plasma Partitioning

The partitioning study (Study # TR-0123) in human whole blood indicated no significant distribution of zilucoplan into the erythrocyte fraction ([Table 65](#)).

Table 65. Blood Partitioning of Zilucoplan

Species	Test article dosing concentration (μM)	RBC to plasma partitioning ($K_{RBC/P}$)	Whole blood to plasma partitioning ($K_{WB/P}$)
Human	2	0.25	0.72
Human	20	0.20	0.70
Human	200	0.37	0.76

RBC=red blood cells; P=plasma; WB=whole blood

Source: Table 4-2 (Pg 19 of 36) from Module 2.6.4 Pharmacokinetics Written Summary

14.1.3. Metabolism of Zilucoplan (Study # 16900, # TR-0160, # TR-0128)

Metabolite radioprofiling and identification and cytochrome P450 (CYP) phenotyping assay indicated two major metabolites, RA102758 (formed by protease mediated degradation), and RA103488 (formed by ω -oxidation by CYP4F2)

Based on metabolite radioprofiling and identification, zilucoplan was stable in human plasma with no metabolite detection up to 8-hour incubation (Study # 16900). The in vitro metabolic profile of zilucoplan evaluated in human hepatocytes indicated peptide hydrolysis as the predominant metabolic pathway. The CYP phenotyping assay in human liver microsomes and recombinant human CYP enzymes indicated that RA103488, the ω -oxidation of zilucoplan, is mainly due to CYP4F2, with minor contributions from CYP4A11, CYP4F3A, and CYP4F3B (Study # TR-0160). Quantitation of metabolites in human plasma (# TR-0128) from First-In-Human (FIH) study (# UP0112) indicated two major metabolites, RA102758 and RA103488. RA102758 is formed by protease mediated degradation of the peptide chain at the terminal amino acid lysine attached to ethylene glycol24-palmitic acid tail of zilucoplan. Whereas RA103488 is formed by ω -hydroxylation of the C16 lipid tail of the parent drug by CYP4F2. It should be noted that the systemic exposure of RA102758 and RA103488 was 10.6% and 9.4% of the systemic exposure of zilucoplan at steady state (0.3 mg/kg/day for 14 days, study # UP0113) indicating overall low exposure of these two metabolites in humans.

14.1.4. Inhibition and Induction of CYP Enzymes by Zilucoplan and Metabolite RA102758 (Study # TR-0102, # 18RAPHP3, # 20RAPHP3, # 20RAPHP5R3)

The in vitro studies as discussed below suggested that zilucoplan and its metabolite RA102758 is not an inhibitor or inducer of major CYP enzymes.

The CYP inhibition potential of zilucoplan and RA102758 (up to a concentration of 100 μ M) was evaluated for major CYP enzymes and CYP4F was evaluated in vitro in human liver microsomes (Study # TR-0102, # 18RAPHP3, #20RAPHP3). Per the results presented in [Table 66](#) (I/Ki for all CYPs less than <0.02), drug-drug interaction due to CYP inhibition by zilucoplan or RA102758 is unlikely. The half maximal inhibitory concentration (IC₅₀) shift assay (#20RAPHP3) results also indicated that there was no time-dependent inhibition of major CYP enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A) by zilucoplan or RA102758. The potential of zilucoplan to induce CYP enzymes (CYP 1A2, 2B6, and 3A4) was evaluated using human hepatocytes ([Table 67](#)). Since there was no increase in mRNA level for the tested CYPs and the fold-change was below twofold, it was concluded that zilucoplan is unlikely an inducer of CYP enzymes tested. The review team agrees with the Applicant's conclusions.

The CYP inhibition and induction potential of metabolite RA103488 was not evaluated. However, it is noted that RA103488 is formed by hydroxylation of the C16 lipid tail of zilucoplan and is therefore structurally similar and is not expected to have a different CYP inhibition or induction profile compared to zilucoplan. Further, the systemic exposure of the metabolite RA103488 is ~10% to that of zilucoplan. The induction potential of metabolite

RA102758 was also not evaluated; however, it is not concerning since the systemic exposure of the RA102758 is also low ~10% to that of zilucoplan.

Table 66. Summary of CYP Isoform Reversible Inhibition by Zilucoplan or RA102758

CYP Isoform	Probe Substrate	Zilucoplan		RA102758	
		IC ₅₀ (μM)	[I]/K _i (μM) ^a	IC ₅₀ (μM)	[I]/K _i (μM) ^a
1A2	Phenacetin (63μM)	79	<0.02	66.6	<0.02
2B6	Bupropion (75μM)	94	<0.02	57.1	<0.02
2C8	Amodiaquine (2μM)	>100	<0.02	62.3	<0.02
2C9	Diclofenac (10μM)	NI	<0.02	>100	<0.02
2C19	S-mephenytoin (40μM)	NI	<0.02	>100	<0.02
2D6	Bufuralol (7μM)	>100	<0.02	84.3	<0.02
3A	Midazolam (2.5μM)	88	<0.02	55.8	<0.02
	Testosterone (55μM)	>100	<0.02	62.7	<0.02
4F	Leukotriene B4 (3μM)	>100	<0.02	>100	<0.02

CYP=Cytochrome P450; IC₅₀=half-maximal inhibitory concentration; NI=no inhibition observed up to the highest concentration tested.

^a [I]/K_i, where estimated K_i=IC₅₀/2 based on the Cheng-Prusoff relationship Ki=IC₅₀/1+[s]/km where km of substrate is equal to the conc [s] used in the assay; [I]=f_a*C_{max}; zilucoplan total C_{max}=12,310ng/mL (ie 3.46μM, MW=3559.97) with fu=0.01; RA102758 total C_{max}=1267ng/mL (ie 0.77μM, MW=1642) (Tables 14.2.2.4 and 14.2.2.5 in RA101495-01.102 clinical study report, geometric mean of Caucasian group on Day 14) with f_a=0.01.

Source: Table 7-2 (Pg 26 of 36) from Module 2.6.4 Pharmacokinetics Written Summary

Table 67. Summary of CYP Induction by Zilucoplan

Donor ^a	Concentration (μM)	1A2		2B6		3A4	
		Mean fold change ^b	% of positive control ^c	Mean fold change ^b	% of positive control ^c	Mean fold change ^b	% of positive control ^c
1	2	0.437	0	1.55	4.57	0.335	0
	6	0.363	0	1.70	5.85	1.63	0.402
	20	0.333	0	1.52	4.38	1.02	0.0120
2	2	0.781	0	0.996	0	2.07 ^d	0.395
	6	0.686	0	0.387	0	1.25	0.0211
	20	0.642	0	1.19	0.619	0.451	0
3	2	0.374	0	0.444	0	0.368	0
	6	0.376	0	0.403	0	0.0221	0
	20	0.338	0	0.793	0	0.0332	0

^a Hepatocytes from different donors were used.

^b Fold-change of mRNA=mRNA_{test article}/mRNA_{vehicle}. Vehicle control: Hepatocytes culture medium for all CYPs.

^c % of positive control=100 × (mRNA_{test article}-mRNA_{vehicle})/(mRNA_{positive control}-mRNA_{vehicle}). Positive controls: omeprazole (50μM) for CYP1A2, phenobarbital (1000μM) for CYP2B6, and rifampicin (50μM) for CYP3A4. Negative control: flumazenil (10μM) for all CYPs.

^d The negative control showed 3.41-fold change in CYP3A4 mRNA level.

Source: Table 7-2 (Pg 27 of 36) from Module 2.6.4 Pharmacokinetics Written Summary

14.1.5. Inhibition of Uridine 5'-Diphospho-Glucuronosyltransferase (UGT) Enzymes (Study # TR-0102)

Based on in vitro studies, any clinically relevant interaction between zilucoplan and uridine diphosphoglucuronosyl transferases (UGT) substrate is not expected.

UGT inhibition by zilucoplan (up to 100µM) was evaluated on UGT 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 human recombinant UGT enzymes ([Table 68](#)). A weak inhibition was observed for UGT1A1 (IC₅₀ 12µM) and 1A3 (IC₅₀ 48µM), while no inhibition greater than 50% was detected for other isoforms at 100µM. These results indicated that a clinically relevant interaction between zilucoplan and substrates of these UGT isoforms is unlikely. The review team agrees with the Applicant's conclusions.

Table 68. Summary of UGT Inhibition by Zilucoplan

Study number	TR-0102						
Study information	In vitro evaluation of zilucoplan as an inhibitor of major human UGT enzymes						
Study system	The potential inhibitory effect of zilucoplan (up to 100µM) was evaluated on recombinant human UGT enzymes, including 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15, in the presence of probe substrate and uridine-5'-diphosphoglucuronic acid. The respective probe substrates used to determine potential inhibition were 7-hydroxy-4-trifluoromethylcoumarin for UGT 1A1, 1A3, 1A6, 1A9, 2B7 and 2B15, and trifluoperazine for UGT1A4						
Enzyme	UGT1A1	UGT1A3	UGT1A4	UGT1A6	UGT1A9	UGT2B7	UGT2B15
IC ₅₀ (µM)	12	48	>100	>100	>100	>100	>100

IC₅₀=half-maximal inhibitory concentration; UGT=uridine 5'-diphospho-glucuronosyltransferase.

Source: Table 12-2 (Pg 53 of 76) from Module 2.6.5 Pharmacokinetics Tabulated Summary

14.1.6. Interaction Potential of Zilucoplan and RA102758 for Drug Transporters (Study # TR-0100, #TR-0101, # TR-0145, Rapharma-12-23Jan2018, and Rapharma-16-22Aug2019)

In vitro studies suggested that zilucoplan is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3 ([Table 69](#)). The substrate potential of zilucoplan for renal transporters (OAT1, OAT3, MATE1/MATE2-K, OCT2) is not evaluated. It is noted that excretion of zilucoplan and its metabolites is negligible (<1% of the dose) and hence lack of these data are not concerning. Based on the above, it is unlikely that zilucoplan will be a victim of inhibitor or inducer of the above transporters. The potential of zilucoplan to inhibit major transporters is low since unbound maximum plasma concentration (C_{max,unbound})/IC₅₀ ratio was lower than 0.02 ([Table 69](#)). The review team agrees with the Applicant's conclusion that a clinically relevant drug-drug interaction due to transporter inhibition by zilucoplan or RA102758 is not expected.

Table 69. Summary of Transporter Interaction of Zilucoplan and RA102758

Transporter	Substrate	IC ₅₀ (μM)	C _{max,unbound} ^a /IC ₅₀
Zilucoplan			
P-gp	No	>100	<0.02
BCRP	No	31.7	<0.02
MATE1	Not evaluated	>50	<0.02
MATE2-K	Not evaluated	>50	<0.02
OATP1B1	No	2.36 (30-minute preincubation)	<0.02
OATP1B3	No	2.12 (30-minute preincubation)	<0.02
OAT1	Not evaluated	>50	<0.02
OAT3	Not evaluated	>50	<0.02
OCT1	Not evaluated	>50	<0.02
OCT2	Not evaluated	>50	<0.02
RA102758			
P-gp	Not evaluated	3.01	<0.02
BCRP	Not evaluated	>50	<0.02
MATE1	Not evaluated	10.82	<0.02
MATE2-K	Not evaluated	>40	<0.02
OATP1B1	No	3.97 (30-minute preincubation)	<0.02
OATP1B3	No	6.58 (30-minute preincubation)	<0.02
OAT1	Not evaluated	>50	<0.02
OAT3	Not evaluated	>50	<0.02
OCT1	Not evaluated	12.49	<0.02
OCT2	Not evaluated	>50	<0.02

BCRP=breast cancer resistance protein; IC₅₀=half-maximal inhibitory concentration; MATE=multi-drug and toxin extrusion protein; NA=not applicable; OAT=organic anion transporter; OATP=organic anion-transporting polypeptide; OCT=organic cation transporter; P-gp=P-glycoprotein

^aZilucoplan total C_{max}=12,310ng/mL (ie 3.46μM, MW=3559.97) with f_u=0.01; RA102758 total C_{max}=1267ng/mL (ie 0.77μM, MW=1642) (Tables 14.2.2.4 and 14.2.2.5 in RA101495-01.102 clinical study report, geometric mean of Caucasian group on Day 14) with f_u=0.01.

Source: Table 7-3 (Pg 28 of 36) from Module 2.6.4 Pharmacokinetics Written Summary

Reviewer's Assessment: The reviewer agrees with the Applicant's assessment and conclusions that clinically relevant interactions between zilucoplan and substrates of CYP enzymes, UGTs, and transporters is unlikely.

14.2. In Vivo Studies

14.2.1. Study # UP0112 – Single Ascending Dose and Multiple Dose Study

Study Design

The study UP0112 was a Phase 1, randomized, placebo-controlled, double-blind, single ascending dose and multiple dose study for the evaluation of safety, tolerability pharmacokinetics (PK), and pharmacodynamics (PD) of zilucoplan in healthy subjects. The single dose cohorts evaluated zilucoplan (n=10 subjects) versus placebo (n=8 subjects) at 4 dose levels (0.05 mg/kg (n=2 subjects), 0.1 mg/kg (n=4 subjects), 0.2 mg/kg (n=4 subjects), and

0.4 mg/kg (n=4 subjects)) administered subcutaneously (SC). The multiple dose cohort evaluated zilucoplan (n=4 subjects) at 0.2 mg/kg administered subcutaneously once daily over 7 days versus placebo (n=2 subjects). Blood samples were collected predose and postdose for the determination of plasma concentrations of zilucoplan and its metabolites (RA102758 and RA103488) and for the measurement of complement activity (sheep red blood cell [sRBC] lysis) and total C5 levels. For single dose cohorts, blood samples for PK were obtained on days 1, 2, 5, 8, 15, 29. Day 1 included collection of samples predose and at 15 minutes, 1-, 3-, 6- and 12-hours postdose. For the multiple dose cohort, blood samples for PK were obtained on day 1 through 7 and at days 8, 15, 21 and 35. days 1 to 7 included a predose collection and at 3 and 6 hours postdose. PD sample collection occurred concurrently with collection of PK samples. All subjects completed the study per protocol.

Results

[Table 70](#) and [Table 71](#) presents zilucoplan PK parameters following single and multiple doses respectively. The exposure of metabolites (RA102758 and RA103488) relative to zilucoplan is presented in [Table 72](#).

Table 70. Summary of Zilucoplan PK Parameters, Single Ascending Dose Cohort (Study # UP0112)

Parameter	Statistic	1/ RA101495 (0.05 mg/kg)	2/ RA101495 (0.10 mg/kg)	3/ RA101495 (0.20 mg/kg)	4/ RA101495 (0.40 mg/kg)
C_{max} (ng/mL)	N	2	4	4	4
	Geometric mean	1010	1540	2958	5860
	Geometric CV (%)	1.4	13.1	10.5	7.6
t_{max} (h)	N	2	4	4	4
	Median	4.5	3.0	4.5	4.6
	SD	2.12	10.50	22.05	1.68
	CV (%)	47.1	127.3	147.0	37.0
AUC_{last}^a (h*ng/mL)	N	2	4	4	4
	Mean	179800	375400	655100	822600
	SD	3214.7	47513	113710	120760
	CV (%)	1.8	12.7	17.4	14.7
AUC_{0-24} (h*ng/mL)	N	2	4	4	4
	Mean	21440	33230	60350	112300
	SD	1020.9	4605.6	4624.8	8623.2
	CV (%)	4.8	13.9	7.7	7.7
K_{el} (1/h)	N	2	4	4	4
	Mean	0.004248	0.003743	0.004092	0.004482
	SD	0.00028369	0.00012848	0.00058001	0.00041984
	CV (%)	6.7	3.4	14.2	9.4
$t_{1/2}$ (h)	N	2	4	4	4
	Mean	163.5	185.4	172.0	155.6
	SD	10.92	6.35	24.76	14.27
	CV (%)	6.7	3.4	14.4	9.2
CL/F (mL/h/kg)	N	2	4	4	4
	Mean	0.2622	0.2481	0.2933	0.4711
	SD	0.0042347	0.035323	0.057378	0.065956
	CV (%)	1.6	14.2	19.6	14.0
Vz/F (mL/kg)	N	2	4	4	4
	Mean	61.89	66.41	71.43	105.1
	SD	5.1303	10.197	7.5150	11.679
	CV (%)	8.3	15.4	10.5	11.1

^a $AUC_{(0-last)}$ is time to the last collection timepoint, Day 29. Source: Table 14.2.1.2.1a

Source: Table 11-2a (Pg 61 of 669) from UP0112 Clinical Study Report

Table 71. Summary of Zilucoplan PK Parameters, Multiple Dose Cohort (Study # UP0112)

Parameter	Statistic	Day 1	Day 7
C _{max} (ng/mL)	N	4	4
	Geometric mean	2531	7266
	Geometric CV (%)	4.0	9.5
t _{max} (h)	N	4	4
	Mean	3.8	3.8
	SD	1.6	1.5
	CV (%)	41.3	40.0
AUC _{tau} ^a (h*ng/mL)	N	4	4
	Mean	50010	151300
	SD	3334	12042
	CV (%)	6.7	8.0
K _{el} (1/h)	N	NA	4
	Mean		0.004309
	SD		0.000413
	CV (%)		9.6
AUC(0-inf) ^b (h*ng/mL)	N	NA	4
	Mean		1101000
	SD		108220
	CV (%)		9.8
t _{1/2} (h)	N	NA	4
	Mean		161.9
	SD		14.8
	CV (%)		9.1
CL/F (mL/h/kg)	N	NA	4
	Mean		1.330
	SD		0.114
	CV (%)		8.6
V _{z_F} (mL/kg)	N	NA	4
	Mean		311.6
	SD		51.5
	CV (%)		16.5
C _{ssave} (ng/mL)	N	NA	4
	Mean		6305
	SD		501.8
	CV (%)		8.0
Accumulation Index	N	NA	4
	Mean		3.03
	SD		0.24
	CV (%)		7.8
%Fluctuation (%)	N	NA	4
	Mean		37.38
	SD		2.35
	CV (%)		6.3

^aAUC_{tau} is area under the drug concentration-time curve over the dosing interval (24 hours), ^bAUC_{last} is calculated from last collection on Day 35.

Source: Table 11-2b (Pg 63 of 669) from UP0112 Clinical Study Report

Table 72. Metabolic Ratio of RA102758 and RA103488 Following the Final SC Administration of 0.2 mg/kg (QD) for 7 Days (Study # UP0112)

Compound	Description	C _{max} (ng/mL, mean)	AUC _{tau} (ng•h/mL, mean)	Metabolic Ratio (%) ^a
ZLP	Parent	7255	151,815	--
RA103488	ω-hydroxylation of ZLP	1147	24,042	16
RA102758	Lys-EG-C16	798	18,419	12

CSR=clinical study report; QD=once daily; ZLP=zilucoplan

Note: UP0112 is a legacy Ra Pharma study, and the data are as reported in the CSR.

Note: No variability parameters were reported.

^a (AUC metabolite/AUC parent) × 100; correction for molecular weight should be made: MW parent/MW metabolite for RA103488 correction factor is 1, for RA102758 correction factor is 2.17. MW parent is 3562.23 Da; MW RA102758-1642.07Da and MW RA103488 is 3578.23 Da

Source: Table 2-3 (Pg 24 of 94) from Summary of Clinical Pharmacology Studies (Module 2.7.2).

Key Conclusions

From single ascending dose cohorts, the peak exposure maximum plasma concentration ($C_{\max}$) and systemic exposure (area under the concentration-time curve, AUC_{0-24}) increased with the increase in dose. The increase in $C_{\max}$ was approximately dose proportional while the increase in AUC was less than dose proportional between 0.05 mg/kg and 0.40 mg/kg. The peak exposure occurred at time ranging from 3 hours to 4.6 hours across all doses. The mean terminal half-life ($t_{1/2}$) ranged from 155.6 hours to 185.4 hours (i.e., approximately 7 days) across all doses.

From multiple dose cohort, following daily dosing of zilucoplan (0.2 mg/kg) for 7 days, $C_{\max}$ and AUC_{τ} (area under the concentration-time curve over the dosing interval of 24 hours) increased by approximately threefold. The terminal half-life ($t_{1/2}$) of zilucoplan at 0.2 mg/kg dose was consistent following single ($t_{1/2}$ =172 hours) and repeat dosing ($t_{1/2}$ =161.9 hours). Steady state was not achieved with 7 days of daily dosing at 0.2 mg/kg; however, based on multiple once daily doses at 0.3 mg/kg in Phase 3 study MG0010, steady state trough concentration of zilucoplan reached by 4 weeks. The systemic exposure (AUC_{0-24}) of metabolites, RA102758 and RA103488, was 12% and 16% respectively when compared to the systemic exposure of zilucoplan.

The Applicant noted that across all dose groups, plasma levels of total C5 increased following a single dose and multiple doses. The mean maximum total C5 levels reached 81 µg/mL, 99 µg/mL, 99 µg/mL, 116 µg/mL postdose following single doses of 0.05, 0.1, 0.20, and 0.40 mg/kg respectively. There were no notable changes observed in C5 concentration across the time points for the placebo groups. For the multiple dose (MD) cohort, 0.2 mg/kg for 7 days, the mean maximum total C5 levels reached 151 µg/mL. The observed increase in C5 is due to the prolongation of the half-life of C5 bound to zilucoplan and not due to increase in available free C5. The Applicant noted that the increases in C5 level coincided with increased plasma level of zilucoplan.

For complement inhibition, the Applicant found that the mean maximum percent inhibition of sRBC lysis compared to baseline reached 52%, 86%, 87%, and 95% postdose following single doses of 0.05, 0.1, 0.2, and 0.4 mg/kg respectively suggesting dose-dependent complement inhibition. Mean sRBC lysis levels remained below baseline for up to 2 days in the 0.05 mg/kg cohort, up to 4 days in the 0.1 mg/kg cohort, and for up to 7 days in the 0.2 and 0.4 mg/kg cohorts. There was no inhibition of sRBC lysis for the pooled placebo group across all time points. For MD cohort, 0.2 mg/kg for 7 days, the mean percent inhibition of sRBC lysis reached >95% after first dosing and continued through the 7 days of dosing. Mean sRBC lysis levels remained below baseline for up to 15 days in the 0.2 mg/kg for MD cohort. It was also noted that the maximum %sRBC lysis inhibition i.e., peak PD effect coincided with the time for peak concentration ($t_{\max}$) of zilucoplan for both single doses and multiple dose cohorts. The overall PK and PD data from this Phase 1 study suggested correlation between PK and complement inhibition.

14.2.2. Study # UP0113 – Ethno-Bridging Study in Japanese and Caucasian Subjects

Study Design

Study UP0113 was a Phase 1, randomized, double-blind study to investigate the safety, tolerability, PK, and PD of single and multiple doses of zilucoplan following SC administration in healthy Japanese and Caucasian subjects. The study consisted of 2 single-dose cohorts (0.1 mg/kg and 0.3 mg/kg; zilucoplan n=4 each, Japanese and white in each cohort; matching placebo n=1 each, Japanese and white in each cohort) and a multiple-dose cohort (0.3 mg/kg; once daily (QD) for 14 days; zilucoplan n=6 each, Japanese and white; matching placebo n=2 each Japanese and white). Blood samples for the determination of plasma concentration of zilucoplan and its metabolites (RA102758 and RA103488) and for the measurement of complement activity (sRBC lysis) and total C5 levels were collected predose, postdose (1, 3, 6, 12, and 24 hours), at study visits (days 7 and 14) post-treatment, and end-of-study (EOS) visit. All subjects completed the study. The Applicant submitted updated PK analysis for zilucoplan, RA1027528, and RA103488 in sequence number (SN)# 0037 upon correction related to the unit of time and PK samples recorded as BLQ.

Results

The PK comparison of zilucoplan, RA102758, and RA103488 between white and Japanese subjects following single and multiple doses are presented in [Table 73](#), [Table 74](#), [Table 75](#), and [Table 76](#).

Table 73. Summary of Zilucoplan PK Parameters in Japanese and White Subjects, Single Dose Cohorts (Study # UP0113)

Dose	PK Parameter	Caucasian			Japanese			Ethnicity Effect (Japanese/Caucasian)	
		N	Geometric Mean	90% CI	N	Geometric Mean	90% CI	Geometric Mean Ratio (%)	90% CI
0.1mg/kg	C _{max} (ng/mL)	4	1670	(1486.24, 1884.49)	4	1610	(1426.71, 1809.01)	95.99	(80.07, 115.09)
	AUC _{0-last} (h*ng/mL)	4	388000	(355458.91, 423176.02)	4	443000	(405682.32, 482967.29)	114.13	(99.89, 130.40)
	AUC _{0-inf} (h*ng/mL)	4	421000	(385373.24, 460072.13)	4	499000	(456610.97, 545118.24)	118.49	(103.48, 135.67)
0.3mg/kg	C _{max} (ng/mL)	4	3540	(3306.45, 3783.56)	4	3810	(3561.34, 4075.24)	107.71	(97.69, 118.75)
	AUC _{0-last} (h*ng/mL)	4	604000	(504606.64, 722830.59)	4	741000	(619355.47, 887204.10)	122.74	(94.62, 159.23)
	AUC _{0-inf} (h*ng/mL)	4	648000	(533262.13, 787340.76)	4	815000	(670777.33, 990376.61)	125.79	(94.86, 166.79)

ANCOVA=analysis of covariance; CI=confidence interval; CSR=clinical study report; N=the number of participants in the Randomized Population in each ethnicity, cohort, treatment group, and overall; PK=pharmacokinetic; ZLP=zilucoplan

Note: UP0113 is a legacy Ra Pharma study, and the data are as reported in the CSR.

Note: An ANCOVA model of the log-transformed PK parameters were used to assess the effect of ethnicity on PK parameters for Japanese vs Caucasian participants using ethnicity as an independent variable and participant Baseline weight as covariate.

Note: PK parameters were the dependent variables.

Note: Placebo participants are excluded from this table as the concentration values of placebo participants are all below limit of quantification.

Source: Table 2-4 (Pg 30 of 94) from Summary of Clinical Pharmacology Studies (Module 2.7.2).

Table 74. Summary of Zilucoplan PK Parameters in Japanese and Caucasian Subjects, Multiple Dose Cohort (Study # UP0113)

Day	Dose	PK Parameter	Caucasian			Japanese			Ethnicity Effect (Japanese/Caucasian)	
			N	Geometric Mean	90% CI	N	Geometric Mean	90% CI	Geometric Mean Ratio	90% CI
1	0.3mg/kg	C _{max} (ng/mL)	6	4090	(3654.88, 4582.74)	6	3930	(3508.69, 4399.43)	96.00	(80.87, 113.97)
		AUC _t (h*ng/mL)	6	81000	(74913.91, 87635.20)	6	79200	(73182.86, 85610.20)	97.69	(86.73, 110.03)
14	0.3mg/kg	C _{max} (ng/mL)	6	12100	(10915.50, 13460.99)	6	13500	(12195.69, 15039.72)	111.73	(95.31, 130.98)
		AUC _{tau} (h*ng/mL)	6	256000	(229306.75, 285665.30)	6	276000	(247239.56, 308005.60)	107.82	(91.27, 127.37)

ANCOVA=analysis of covariance; CI=confidence interval; CSR=clinical study report; N=the number of participants in the Randomized Population in each ethnicity, cohort, treatment group, and overall; QD=once daily; SC=subcutaneous; SD=standard deviation PK=pharmacokinetic; ZLP=zilucoplan

Note: UP0113 is a legacy Ra Pharma study, and the data are as reported in the CSR.

Note: An ANCOVA model of the log-transformed PK parameters were used to assess the effect of ethnicity on PK parameters for Japanese vs Caucasian participants using ethnicity as an independent variable and participant Baseline weight as covariate.

Note: PK parameters were the dependent variables.

Note: Placebo participants are excluded from this table as the concentration values of placebo participants are all below limit of quantification.

Source: Table 2-6 (Pg 36 of 94) from Summary of Clinical Pharmacology Studies (Module 2.7.2).

Table 75. Summary of RA102758 and RA103488 PK Parameters in Japanese and Caucasian Subjects, Single Dose Cohorts (Study # UP0113)

Metabolite	Dose	PK Parameter	Caucasian			Japanese			Ethnicity Effect (Japanese/Caucasian)	
			N	Geo Mean	90% CI	N	Geo Mean	90% CI	Geo Mean Ratio (%)	90% CI
RA103488	0.1mg/kg	C _{max} (ng/mL)	4	38.4	(32.06, 45.89)	4	31.4	(26.26, 37.60)	81.93	(62.28, 107.77)
		AUC _{0-last} (h*ng/mL)	4	18,600	(15503.98, 22321.09)	4	15600	(13014.30, 18736.69)	83.94	(63.53, 110.90)
	0.3mg/kg	C _{max} (ng/mL)	4	214	(161.99, 282.33)	4	134	(101.24, 176.45)	62.50	(41.80, 93.45)
		AUC _{0-last} (h*ng/mL)	4	86,500	(68608.76, 108988.32)	4	60200	(47736.55, 75831.81)	69.58	(49.76, 97.28)
RA102758	0.3mg/kg	C _{max} (ng/mL)	4	61.4	(50.57, 74.52)	4	93.4	(76.97, 113.44)	152.22	(114.95, 201.59)
		AUC _{0-last} (h*ng/mL)	4	10,900	(8150.03, 14703.71)	4	22100	(16419.88, 29623.59)	201.47	(131.41, 308.87)

ANCOVA=analysis of covariance; CI=confidence interval; CSR=clinical study report; Geo=geometric; N=the number of participants in the Randomized Population in each ethnicity, cohort, treatment group, and overall; PK=pharmacokinetic(s); ZLP=zilucoplan

Note: UP0113 is a legacy Ra Pharma study, and the data are as reported in the CSR.

Note: An ANCOVA model of the log-transformed PK parameters were used to assess the effect of ethnicity on PK parameters for Japanese vs Caucasian participants using ethnicity as an independent variable and participant Baseline weight as covariate.

Note: PK parameters were the dependent variables.

Note: Placebo participants were excluded from this table as the concentration values of placebo participants were all below limit of quantification.

Source: Table 2-5 (Pg 31 of 94) from Summary of Clinical Pharmacology Studies (Module 2.7.2).

Note. Geometric mean concentrations over time of RA102758 following a single 0.1 mg/kg dose were mostly below the lower limit of quantification (LLOQ) for Japanese and white subjects. Therefore, PK parameters for RA102758 following single dose administration of zilucoplan is not reported in the above table.

Table 76. Summary of RA102758 and RA103488 PK Parameters in Japanese and Caucasian Subjects, Multiple Dose Cohort (Study # UP0113)

Metabolite	Dose	PK Parameter	Caucasian			Japanese			Ethnicity Effect Japanese/Caucasian	
			N	Geometric Mean	90% CI	N	Geometric Mean	90% CI	Geometric Mean Ratio (%)	90% CI
RA103488	0.3m/kg (Day 1)	C _{max} (ng/mL)	6	84.5	(69.92, 102.14)	6	60	(49.66, 72.55)	71.03	(53.29, 94.68)
		AUC _{0-τ} (h*ng/mL)	6	923	(740.04, 1150.57)	6	642	(514.25, 800.05)	69.54	(49.76, 97.17)
	0.3mg/kg (Day14)	C _{max} (ng/mL)	6	1100	(899.59, 1339.05)	6	903	(739.78, 1101.17)	82.24	(60.82, 111.19)
		AUC _{0-τ} (h*ng/mL)	6	24,700	(20605.72, 29489.91)	6	19,200	(16074.68, 23005.30)	78.01	(59.44, 102.38)
RA102758	0.3m/kg (Day 1)	C _{max} (ng/mL)	6	49.3	(42.78, 56.76)	6	51.1	(44.36, 58.86)	103.69	(83.68, 128.49)
		AUC _{0-τ} (h*ng/mL)	6	476	(411.23, 551.02)	6	507	(437.79, 586.60)	106.46	(85.27, 132.91)
	0.3mg/kg (Day14)	C _{max} (ng/mL)	6	1260	(1038.84, 1532.03)	6	1620	(1331.52, 1963.64)	121.17	(95.47, 172.08)
		AUC _{0-τ} (h*ng/mL)	6	28,000	(23145.12, 33767.72)	6	34800	(28817.16, 42042.99)	124.51	(93.50, 165.80)

ANCOVA=analysis of covariance; CI=confidence interval; CSR=clinical study report; N=the number of participants in the Randomized Population in each ethnicity, cohort, treatment group, and overall; PK=pharmacokinetic; SC=subcutaneous; QD=once a day; ZLP=zilucoplan

Note: UP0113 is a legacy Ra Pharma study, and the data are as reported in the CSR.

Note: An ANCOVA model of the log-transformed PK parameters were used to assess the effect of ethnicity on PK parameters for Japanese vs Caucasian participants using ethnicity as an independent variable and participant Baseline weight as covariate.

Note: PK parameters were the dependent variables.

Note: Placebo participants were excluded from this table as the concentration values of placebo participants were all below limit of quantification.

Source: Table 2-7 (Pg 37 of 94) from Summary of Clinical Pharmacology Studies (Module 2.7.2); and Updated PK Analysis (SN # 0037)

Note. This table is reviewer generated table that combines information/data provided in original submission (SN # 0001) and updated PK analysis (SN # 0037)

Key Conclusions

Geometric mean concentrations over time of zilucoplan, RA103488, and RA102758 and the statistical analyses to assess the effect of ethnicity on exposure parameters (C_{max} and AUC) indicated that PK was generally similar for Japanese and white subjects following single (0.1 mg/kg and 0.3 mg/kg) and multiple (0.3 mg/kg, QD for 14 days) doses of zilucoplan. The updated PK analysis provided by the Applicant (SN # 0037) for zilucoplan (single dose and multiple dose), RA102758 (multiple dose), and RA103488 (multiple dose) did not impact the conclusion for the ethnicity assessment. The exposure of the 2 metabolites is low compared to zilucoplan (White ----- RA102758 – 10.6% of zilucoplan exposure; RA103488 – 9.4% of zilucoplan exposure; Japanese ----- RA102758 – 12.6% of zilucoplan exposure; RA103488 – 6.9% of zilucoplan exposure). The PD effects (total C5 levels, and %RBC lysis) of zilucoplan was also similar between Japanese and white subjects following single (0.1 mg/kg and 0.3 mg/kg) and multiple (0.3 mg/kg, QD for 14 days.) doses of zilucoplan. It is noted that any labeling claim based on the above ethnicity assessment is not made by the Applicant.

14.2.3. Study # UP0114 – Renal Impairment Study

Study Design

Study UP0114 was a Phase 1, open-label study to assess the PK of zilucoplan and its metabolites (RA102758 and RA103488) in subjects with severe renal impairment (estimated creatinine clearance <30 mL/min based on Cockcroft-Gault formula; n=8) and matched (with respect to age, sex, body mass index) healthy subjects with normal renal function (n=8) after administration of a single subcutaneous (SC) dose of 0.3 mg/kg. Blood samples for PK analysis were collected predose and at 1, 2, 4, 8, 12, 48, 72, 96, and 120 hours after the SC injection, as well as at day 15, 22, 29, and 36 visits. Pooled urine collections were tested for concentrations of zilucoplan and its metabolites at predose, 0 to 14 hours, 24 to 48 hours, and 48 to 120 hours. The PD

assessment included the measurement of levels of total C5 predose, and at day 3 and day 6 postdose. All subjects completed the study per protocol.

Results

The PK of zilucoplan, and its metabolites and PD as measured by total C5 levels are summarized in [Table 77](#) and [Table 78](#).

Table 77. Summary of PK for Zilucoplan (RA101495) and Its Metabolites (RA102758 and RA103488) (Renal Impairment Study # UP0114)

Parameter (unit)	Statistic	RA101495		RA102758		RA103488	
		Normal (n=8)	Severe (n=8)	Normal (n=8)	Severe (n=8)	Normal (n=8)	Severe (n=8)
C _{max} (ng/mL)	Mean	4902.50	4482.50	120.35	108.10	182.88	266.88
	SD	910.318	383.881	22.448	30.479	42.286	43.245
	Ratio	0.9251 (0.8161, 1.0487)		0.8827 (0.7215, 1.0801)		1.4731 (1.2522, 1.7330)	
AUC _{0-last} (h*ng/mL)	Mean	801,000.0	703,875.0	24,012.5	25,000.0	85,212.5	127,387.5
	SD	152,645.25	109,321.85	8726.39	9165.15	22,092.43	31,717.97
	Ratio	0.8813 (0.7578, 1.0250)		1.0367 (0.7550, 1.4236)		1.4797 (1.1536, 1.8980)	
AUC _{0-inf} (h*ng/mL)	Mean	836,875.0	725,875.0	26,857.1	23,650.0	104,975.0	147,316.7
	SD	183,169.27	116,135.93	10,579.68	7318.70	34,999.38	46,762.82
	Ratio	0.8730 (0.7414, 1.0278)		0.9071 (0.6032, 1.3640)		1.3821 (0.9871, 1.9353)	

Ratio is the ratio of the geometric least-square means (normal vs severe) reported as the point estimate (90% confidence interval); 1 indicates no change.

* n is lower for AUC_{0-inf} due to the extrapolated AUC (AUC_{extrap}) being >20%: 7 normal vs 4 severe for RA102758, and 8 normal vs 6 severe for RA103488.

Source: Table S1 (Pg 10 of 396) from UP0114 Clinical Study Report

Table 78. Summary of Complement Component C5 Concentrations (Renal Impairment Study # UP0114)

Statistic	Normal (n=8)			Severe (n=8)		
	Day -1	Day 3	Day 6	Day -1	Day 3	Day 6
Mean (µg/mL)	80.375	96.083	116.19	96.088	104.42	125.99
SD (µg/mL)	15.3745	16.4284	21.6672	12.0772	25.9126	23.0332
%CV	19	17	19	13	25	18
Median (µg/mL)	85.665	88.430	112.31	94.050	115.18	130.78
Minimum (µg/mL)	56.48	81.91	86.52	83.65	61.44	92.23
Maximum (µg/mL)	100.19	124.51	152.51	118.59	129.07	161.79
Geometric Mean (µg/mL)	78.957	94.926	114.43	95.453	101.14	124.02
Geometric %CV	21	17	19	12	29	20

SD=standard deviation; %CV=coefficient of variation in percent

Source: Table S2 (Pg 11 of 396) from UP0114 Clinical Study Report

Key Conclusions

The PK of zilucoplan and metabolite RA102758 is generally similar between subjects with severe renal impairment and healthy subjects. For metabolite RA103488, AUC_{0-inf} and C_{max} was 1.4- to 1.5-fold higher in subjects with severe renal impairment respectively as compared to subjects with normal renal function. However, since the exposure of RA103488 is approximately 10% of zilucoplan exposure at steady state (Study # UP0112 and # UP0113), the clinical impact of the observed increase in exposure for RA103488 is expected to be negligible. Further, the total C5 levels were similar across two populations. The urine analysis indicated minimal renal excretion of zilucoplan and metabolites (<1% of dose in total across all analytes). Therefore, the

review team agrees with the Applicant's labeling proposal that no dose adjustment is required for subjects with renal impairment.

14.2.4. Study # UP0094 – Hepatic Impairment Study

Study Design

Study UP0094 was a Phase 1, open-label study to assess the PK of zilucoplan and its metabolites (RA102758 and RA103488) in subjects with moderate hepatic impairment (Child-Pugh category B with a score of 7 to 9; n=8) and matched (with respect to age, sex, body mass index) healthy subjects with normal hepatic function (n=8) after administration of a single subcutaneous (SC) dose of 0.3 mg/kg. Blood samples for PK analysis were collected predose and on days 1, 2 to 6, 15, 22, 29, and 36 after the SC injection. Feces was collected for PK on day 1 and day 2 to day 6. The PD assessment included the measurement of total C5 levels sRBC lysis predose, and 48 hours and 120 hours postdose at day 3, and day 6 postdose and at the EOS. All subjects completed the study per protocol.

Results

The statistical assessment of the effect of hepatic impairment on PK of zilucoplan and its metabolites are summarized in [Table 79](#), [Table 80](#), and [Table 81](#).

Table 79. Statistical Assessment of Effect of Hepatic Impairment on Zilucoplan PK Parameters (Hepatic Impairment Study # UP0114)

Parameter	Arm	N	n	Geo LSMEAN	95% CI	Ratio	Ratio of Geo LSMeans	90%CI	ANOVA CV (%)
AUC _(0-inf) (h*ng/mL)	Moderate HIP	8	8	581400	(509500, 663500)	Moderate HIP/Normal	0.76	(0.65, 0.88)	17.5
	Normal	8	8	769900	(674700, 878600)				
AUC _(0-inf) (h*ng/mL)	Moderate HIP	8	8	594500	(519700, 680200)	Moderate HIP/Normal	0.76	(0.65, 0.88)	17.9
	Normal	8	8	787000	(687900, 900300)				
C _{max} (ng/mL)	Moderate HIP	8	8	4867	(4282, 5533)	Moderate HIP/Normal	0.95	(0.82, 1.10)	17.0
	Normal	8	8	5128	(4511, 5828)				
CL/F ([mL/min]/kg)	Moderate HIP	8	8	0.008415	(0.007354, 0.009630)	Moderate HIP/Normal	1.32	(1.13, 1.55)	17.9
	Normal	8	8	0.006354	(0.005552, 0.007271)				

ANOVA=analysis of variance; CI=confidence interval; CV=coefficient of variation; Geo LSMean=geometric least squares mean; HIP=hepatically impaired

Note: n=number of study participants in category

Note: N=number of study participants in respective arm (Moderate HIP, Normal)

Note: PK parameter was included in the statistical analysis if at least two-thirds of the total observations were available.

Note: ANOVA is used to test the significance of the effects of arm (moderate HIP study participants versus the control group of healthy study participants).

Source: Table 8-4 (Pg 63 of 82) from UP0094 Clinical Study Report

Table 80. Statistical Assessment of Effect of Hepatic Impairment on RA102758 PK Parameters (Hepatic Impairment Study # UP0114)

Parameter	Arm	N	n	Geo LSMEAN	95% CI	Ratio	Ratio of Geo LSMeans	90%CI	ANOVA CV (%)
AUC _(0-last) (h*ng/mL)	Moderate HIP	8	8	24830	(18800, 32810)	Moderate HIP/Normal	1.09	(0.79, 1.50)	38.0
	Normal	8	8	22810	(17260, 30130)				
C _{max} (ng/mL)	Moderate HIP	8	8	152.0	(127.7, 181.0)	Moderate HIP/Normal	1.21	(0.99, 1.48)	23.3
	Normal	8	8	125.6	(105.5, 149.5)				

ANOVA=analysis of variance; CI=confidence interval; CV=coefficient of variation; Geo LSMEAN=geometric least squares mean; HIP=hepatically impaired

Note: n=number of study participants in category

Note: N=number of study participants in respective arm (Moderate HIP, Normal)

Note: PK parameter was included in the statistical analysis if at least two-thirds of the total observations were available.

Note: ANOVA is used to test the significance of the effects of arm (moderate HIP study participants versus the control group of healthy study participants).

Source: Table 8-5 (Pg 65 of 82) from UP0094 Clinical Study Report

Table 81. Statistical Assessment of Effect of Hepatic Impairment on RA103488 PK Parameters (Hepatic Impairment Study # UP0114)

Parameter	Arm	N	n	Geo LSMEAN	95% CI	Ratio	Ratio of Geo LSMeans	90%CI	ANOVA CV (%)
AUC _(0-last) (h*ng/mL)	Moderate HIP	8	8	126600	(106500, 150500)	Moderate HIP/Normal	1.22	(1.00, 1.50)	23.1
	Normal	8	8	103400	(86990, 122900)				
C _{max} (ng/mL)	Moderate HIP	8	8	270.8	(229.6, 319.3)	Moderate HIP/Normal	1.16	(0.96, 1.41)	22.0
	Normal	8	8	233.0	(197.6, 274.7)				

ANOVA=analysis of variance; CI=confidence interval; CV=coefficient of variation; Geo LSMEAN=geometric least squares mean; HIP=hepatically impaired

Note: n=number of study participants in category

Note: N=number of study participants in respective arm (Moderate HIP, Normal)

Note: PK parameter was included in the statistical analysis if at least two-thirds of the total observations were available.

Note: ANOVA is used to test the significance of the effects of arm (moderate HIP study participants versus the control group of healthy study participants).

Source: Table 8-6 (Pg 67 of 82) from UP0094 Clinical Study Report

Key Conclusions

The peak exposure C_{max} of zilucoplan was similar between moderate hepatic impairment and normal subjects. The systemic exposure (AUC_{0-inf}) of zilucoplan was 24% lower in subjects with moderate hepatic impairment compared with subjects with normal hepatic function and associated increase in clearance is observed. The peak exposure and systemic exposure for both metabolites also increased in moderate hepatic impairment subjects compared to normal subjects ranging from 9% to 22%. The total C5 levels and sRBC lysis was similar across two populations.

The observed decrease in systemic exposure of zilucoplan in moderate hepatic impairment subjects is not expected to be clinically significant. There was no meaningful difference identified with respect to total C5 levels and complement inhibition (sRBC lysis) between moderate hepatic impairment subjects and normal subjects despite a 24% lower zilucoplan systemic exposure in moderate hepatic impairment subjects. The review team agrees with the Applicant's conclusions and accordingly, no dose adjustment in subjects with mild and moderate hepatic impairment is required. For subjects with severe hepatic impairment, it will be proposed to the Applicant to include the following language in section 12.3 of labeling "The pharmacokinetics of zilucoplan in patients with severe hepatic impairment have not been studied."

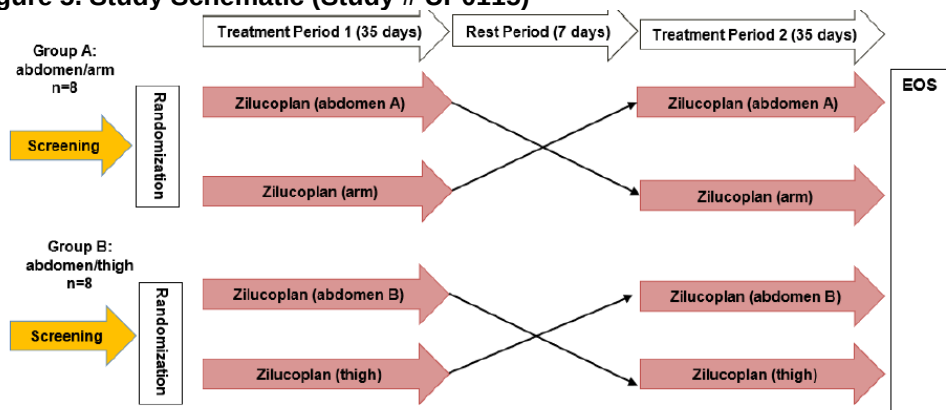
Based on the concentrations of zilucoplan and metabolites in feces and the estimated fraction excreted by the fecal route, zilucoplan was minimally excreted in both the normal and in the moderate hepatic impairment subjects (<1% of dose in total).

14.2.5. Study # UP0115 – Relative Bioavailability Study (Impact of Injection Sites)

Study Design

Study UP0115 was a Phase 1, single-center, randomized, open-label, two-way incomplete cross over study in healthy subjects to assess the relative bioavailability of a single subcutaneous injection of zilucoplan (0.3 mg/kg) at three different sites (abdomen [reference site], thigh, and upper arm) and to evaluate the potential impact of different injection sites on PK and PD of zilucoplan. The incomplete crossover design allowed each subject to receive a single injection of zilucoplan in two of the three different injection sites. The study schematic is presented in [Figure 5](#). There were eight subjects in each Group, A (abdomen/arm) and B (abdomen/thigh). The PK sampling time points were: predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose and on days 3, 5, 8, 15, 22, 29, and 35 postdose. The PD sampling time points for sRBC lysis were: predose and at 1, 3, 6, 24, and 96 hours postdose and on days 15 and 35 postdose.

Figure 5. Study Schematic (Study # UP0115)



EOS=End of Study; n=number of study participants
Source: Table 3-2 (Pg 29 of 97) from UP0115 Clinical Study Report

Results

The statistical assessment for the impact on injection site on PK and PD of zilucoplan are summarized in [Table 82](#) and [Table 83](#).

Table 82. Statistical Analysis of the Effect of Injection Sites on Zilucoplan Plasma PK Parameters (Relative Bioavailability Study # UP0115)

Parameter	Injection site	n	Geo LSMean	95% CI	Ratio (Arm/Abdomen)		
					Estimate	90% CI	ANOVA CV ^a (%)
C _{max} (ng/mL)	Abdomen (A)	7	5472	(4607, 6500)	0.9579	(0.8803, 1.042)	6.94
	Arm (C)	7	5242	(4413, 6226)			
AUC _{0-t} (h*ng/mL)	Abdomen (A)	7	827500	(787200, 869800)	0.9776	(0.9260, 1.032)	4.71
	Arm (C)	7	808900	(769600, 850300)			
C _{max} (ng/mL)	Abdomen (B)	8	5905	(5137, 6787)	0.8642	(0.8017, 0.9316)	7.74
	Thigh (D)	8	5103	(4440, 5865)			
AUC _{0-t} (h*ng/mL)	Abdomen (B)	8	903400	(781400, 1044000)	0.9700	(0.9347, 1.007)	3.81
	Thigh (D)	8	876300	(757900, 1013000)			

ANOVA=analysis of variance; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the last time point with a quantifiable concentration;

C_{max}=maximum plasma concentration; CI=confidence interval; CV=coefficient of variation; Geo=geometric; LSMean=least-squares mean;

PKS=Pharmacokinetic Set; ZLP=zilucoplan

Note: During each treatment period, Group A study participants received 1 injection in either the abdomen (labeled "Abdomen (A)" above) or arm in a randomized order.

Note: The Abdomen A and Arm injection sites were imbalanced in the number of study participants per Treatment Period; this was accounted for in the geo LSMean.

Note: During each treatment period, Group B study participants received 1 injection in either the abdomen (labeled "Abdomen (B)" above) or thigh in a randomized order.

^a Intra-individual CV

Source: Table 8-2 and 8-3 (Pg 75-76 of 97) from UP0115 Clinical Study Report

Table 83. Statistical Analysis of the Effect of Injection Sites on Zilucoplan PD (sRBC Lysis) Parameters (Relative Bioavailability Study # UP0115)

Parameter	Injection site	n	Geo LSMean	95% CI	Ratio (Arm/Abdomen)		
					Estimate	90% CI	ANOVA CV ^a (%)
AUEC _{0-t} (h*%)	Abdomen (A)	7	19650	(18190, 21220)	0.9696	(0.9099, 1.033)	5.34
	Arm (C)	7	19050	(17640, 20580)			
Inhibition _{max} (%)	Abdomen (A)	7	94.68	(93.05, 96.33)	1.002	(0.9974, 1.006)	0.356
	Arm (C)	7	94.84	(93.21, 96.50)			
AUEC _{0-t} (h*%)	Abdomen (B)	7	20600	(19520, 21730)	0.9817	(0.9322, 1.034)	4.89
	Thigh (D)	8	20220	(19240, 21250)			
Inhibition _{max} (%)	Abdomen (B)	7	94.40	(93.36, 95.45)	1.004	(0.9946, 1.013)	0.857
	Thigh (D)	8	94.75	(93.77, 95.74)			

ANOVA=analysis of variance; AUEC_{0-t}=area under the effect curve (inhibition curve of the parameter) from time 0 to time t, where time may be the last time point or earlier to the maximum inhibition; CI=confidence interval; CV=coefficient of variation; FAS=Full Analysis Set; Geo=geometric;

Inhibition_{max}=maximum percentage inhibition of lysis activity expressed from Baseline; LSMean=least-squares mean; RBC=red blood cell

Note: During each treatment period, Group A study participants received 1 injection in either the abdomen (labeled "Abdomen (A)" above) or arm in a randomized order.

Note: The Abdomen A and Arm injection sites were imbalanced in the number of study participants per Treatment Period; this was accounted for in the geo LSMean.

Note: During each treatment period, Group B study participants received 1 injection in either the abdomen (labeled "Abdomen (B)" above) or thigh in a randomized order.

^a Intra-individual CV

Source: Table 8-4 and 8-5 (Pg 81-82 of 97) from UP0115 Clinical Study Report

Key Conclusions

There were no notable differences in peak (C_{max}) and systemic (AUC_{0-t}) exposure of zilucoplan between abdomen and arm injection sites or between abdomen and thigh injection sites. For both C_{max} and AUC_{0-t}, the geometric least squares mean ratio for the comparison of arm versus abdomen and thigh versus abdomen was close to 1 with 90% CI within criteria of 80% to 125%.

The results for PD parameters of sRBC lysis also suggested the same conclusion. The above findings support the administration instruction in the labeling “Administer ZILBRYSQ subcutaneously into areas of the abdomen, thighs, or back of the upper arms.”

14.3. Bioanalytical Method Validation and Performance

14.3.1. Pharmacokinetic Bioanalytical Methods

Zilucoplan and metabolite (RA102758, and RA103488) exposures in plasma, urine, and feces (as applicable in relevant study) were determined using liquid chromatography mass spectrometry (LC-MS/MS). The LC-MS/MS methods as outlined in [Table 84](#) were validated for their use in analyzing samples obtained from Phase 1, 2, and 3 clinical studies. These methods were validated for standard calibration curve and quality control (QC) performance (accuracy and precision); recovery; selectivity; matrix effect; interference and specificity; hemolysis effect; lipemic effect; dilution integrity; bench-top/process stability; freeze-thaw stability; long-term storage stability; stability in processed extract samples; stock solution stability; reinjection stability in extracts; whole blood stability; and carry over. The method performance during the study sample analysis was also evaluated by standard curve and QC performance and method reproducibility (incurred sample reanalysis) assessment.

Table 84. Summary of PK Bioanalytical Methods

	Method # 1	Method # 2	Method # 3	Method # 4	Method # 5
Validation Report #	(b) (4) up0112-16-1-10-2-val160	(b) (4) 302492QB03	(b) (4) 302492QB04	(b) (4) 327049QB10	(b) (4) 1004606
Biological Matrix	Plasma	Plasma	Urine	Feces	Plasma Ultracentrifugate
Analytical Technique	Protein precipitation, LC-MS/MS	Protein precipitation, LC-MS/MS	Solid phase extraction, LC-MS/MS	Solid phase extraction, LC-MS/MS	Protein precipitation, LC-MS/MS
Quantification Range					
Zilucoplan	10.0 to 10,000ng/mL	10.0 to 25,000ng/mL	10.0 to 25,000ng/mL	10.0 to 10,000ng/mL	5.00 to 2000ng/mL
RA102758	N/A	10.0 to 15,000ng/mL	10.0 to 15,000ng/mL	10.0 to 10,000ng/mL	N/A
RA103488	N/A	10.0 to 25,000ng/mL	10.0 to 25,000ng/mL	10.0 to 10,000ng/mL	N/A

	Method # 1	Method # 2	Method # 3	Method # 4	Method # 5
Studies Supported	UP0112	UP0113 UP0114 UP0115 UP0093 UP0094 MG0009 MG0010 MG0011	UP0114	UP0094	UP0094

Source: Table 1-3 and 1-4 (Pg 7-8 of 93) from Module 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods

Reviewer's Assessment: Per FDA's bioanalytical method validation guidance (May 2018), the methods met the requirements for all tested validation parameters. The PK bioanalytical method validation and sample analyses reports are acceptable. Overall, zilucoplan and metabolites concentrations measured in plasma, urine, and feces samples from Phase 1, 2, and 3 studies are reliable.

14.3.2. Pharmacodynamic Bioanalytical Methods

A plasma total C5 assay and sRBC lysis assay used for PD measurement in Phase 1, 2, and 3 clinical studies were based on an enzyme linked immunosorbent assay (ELISA) and hemolysis of activated ovine erythrocytes respectively. The summary of these PD methods is provided in [Table 85](#). The fit for purpose PD assay validation was conducted for all PD assays in [Table 85](#).

Table 85. Summary of PD Bioanalytical Methods

	C5 ELISA	C5 ELISA	sRBC Lysis	sRBC Lysis
Validation Report #	(b) (4) VAL170	(b) (4) 618811	(b) (4) VAL166	(b) (4) 616688
Biological Matrix	Plasma	Plasma	Plasma	Plasma
Analytical Technique	ELISA	ELISA	Hemolysis of Ovine Erythrocytes	Hemolysis of Ovine Erythrocytes
Quantification Range	0.313 to 20.0ng/mL (4.382 to 280µg/mL)	0.6 to 18.0ng/mL (6 to 1,440µg/mL)	1.44 to 90.2% hemolysis	2.00 to 100% Hemolysis
Studies Supported	UP0112	UP0113 UP0114 UP0093 UP0094 MG0009 MG0010 MG0011	UP0112	UP0113 UP0115 UP0094 MG0009 MG0010 MG0011

Source: Table 1-5 and 1-6 (Pg 10-11 of 93) from Module 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods

14.3.2.1. Total C5 Bioanalytical Method

The total C5 method is based on a commercially available human C5 ELISA kit which is compatible with human plasma. The C5 present in the sample is captured by anti-C5 polyclonal capture antibody precoated on 8-well strips. The bound C5 is detected by biotinylated anti-C5 polyclonal antibody and peroxidase-labeled streptavidin and developed with peroxidase substrate. The optical density at 450 nm) measured is proportional to the quantity of C5 in the sample. The total C5 concentration in test samples is derived from the standard curve (7 standard calibrators), and the results are reported as $\mu\text{g/mL}$ of C5. The method's specificity for endogenous C5 level in human plasma is validated to a range of $6\mu\text{g/mL}$ to $1440\mu\text{g/mL}$ (Method 618811). For the context of use, the total C5 ELISA method was validated for QC performance (precision), sensitivity, linearity, hemolysis effect, bench-top/process stability, freeze-thaw stability, long-term storage stability, and parallelism. The C5 in plasma was stable for 90 days at -70°C . The method performance during the study sample analysis was also evaluated by QC performance (precision).

Reviewer's Assessment: For the context of use, the tested validation parameters for total C5 assay method is appropriate to establish its use for sample analysis. The QC precision across 3 levels during validation was $<20\%$. The precision observed during method performance across 3 levels of QC ranged from 11.87% to 23.64% . It was noted that the method validation did not include accuracy and precision for calibration curve performance. In response (received on June 7, 2023, SN # 0042) to the information request (IR; sent on May 31, 2023), the Applicant clarified that monitoring of the accuracy and precision of the calibration curve during validation and sample analysis is not an assay acceptance criterion. Instead, calibration curve acceptance criteria as defined in the associated laboratory standard procedures were: STD7 must be within $\pm 10\%$ of the nominal concentration; curve correlation coefficient $R^2 \geq 0.985$; replicate wells CVOD Corr $\leq 15.0\%$. Further, the Applicant stated that human C5 standard provided in the kit is pre-prepared and not modified during the analytical procedure. The target and measured total C5 for 5 levels of standard calibrators provided by the Applicant in the IR response suggested relative bias $<26\%$ (calculated by the reviewer). Considering the context of use, the Applicant's approach of the procedural verification of the calibration curve characteristics in combination with monitoring and reporting of the QC performance data are considered adequate. The total C5 samples were analyzed within the established stability window. Overall, the total C5 ELISA method validation and sample analyses reports **APPEARS THIS WAY ON ORIGINAL** are acceptable.

14.3.2.2. sRBC Lysis Bioanalytical Method

For Phase 1 and 3 clinical studies, a semiquantitative method was used to test complement activation or inhibition by quantitation of hemolysis of sRBC. Complement activation or inhibition was determined by the degree of hemolysis of activated ovine erythrocytes upon exposure to plasma diluted in gelatin veronal buffer containing Ca^{2+} and Mg^{2+} (GVB++), relative to the control plasma. The diluted plasma samples are incubated with activated ovine erythrocytes (also diluted in GVB++) at 1% final plasma content in a 37°C incubator for 60 minutes. Erythrocytes are pelleted, and the optical density of supernatant (at 412 nm) is read. Percent hemolysis is obtained by subtracting the negative control background and normalizing versus the positive plasma control sample. A low percent hemolysis is indicative of complement

inhibition. The method was validated over the hemolysis range of 2% to 100% (Method 616688). For the context of use, the sRBC lysis method was validated for QC performance (precision), hemolysis effect, bench-top/process stability, freeze-thaw stability, and long-term storage stability. There is no calibration curve for this semiquantitative method. The complement activation by percent lysis in K2 EDTA plasma was stable for 785 days at -70°C. The method performance during the study sample analysis was also evaluated by QC performance (precision).

Reviewer's Assessment: Considering the context of use, the tested validation parameters for %sRBC lysis is appropriate to establish its use for sample analysis. The QC precision across three levels during validation was <20%. The precision observed during method performance across 3 levels of QC ranged from 10.05% to 32.07%. In response (received on June 7, 2023, SN # 0042) to the information request (IR; sent on May 31, 2023), the Applicant clarified that the reference to 'measured concentration (ng/dL)' in Tables 8.7.1 and 8.7.2 in report 616688rep is confirmed to be in error and should correctly read as 'Measured %sRBC Lysis' and the stability data presented in the report are correct. The samples for %sRBC lysis were analyzed within the established stability window. Overall, the %sRBC lysis method validation and sample analyses reports are acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Zilucoplan is a 15 amino acid peptide, and it includes an ethylene glycol moiety. Although zilucoplan is smaller in size compared to protein, it could induce immunogenicity due to peptide and polyethylene glycol (PEG) moiety. Therefore, immunogenicity potential for zilucoplan was monitored by assessing both antidrug antibodies (ADA) and anti-PEG antibody (APA) in Phase 3 (MG0010, and MG0011 [open-label extension study]) studies and its impact on PK, PD, efficacy, and safety was studied. The immunogenicity (ADA response) was also evaluated in the Phase 2 study (MG0009); however, due to the drug interference in immunogenicity assay, the drug tolerance requirements were not met. The immunogenicity assay was further optimized for the Phase 3 study. Therefore, immunogenicity assessment is solely based on data from two Phase 3 studies (MG0010, and MG0011). It should also be noted that the development of assay to detect neutralizing antibody failed due to poor sensitivity and poor target and drug tolerance and hence the impact of neutralizing antibody was not evaluated. The review team opines that the neutralizing antibody assay is not needed since as presented and discussed below (1) the incidence of subjects who develop ADA and APA to zilucoplan is low which is consistent with its predicted immunogenicity potential; and (2) no changes in PK and PD were observed over time.

In study MG0010, baseline samples were collected followed by predose sampling at day 29 (week 4) and day 84 (week 12) for immunogenicity assessment (ADA and APA). In addition to efficacy and safety assessment, PK and PD samples were also collected at the above timepoints to monitor the impact of immunogenicity on zilucoplan PK, PD, efficacy, and safety. The sampling plans are appropriate for the immunogenicity assessment.

ADAs and APAs were detected using a tiered approach involving screening, confirmatory, and titer assays. ADA and APA were measured using a validated direct immune binding assays

which were assessed by the Office of Biotechnology Products (OBP; Refer to OBP's immunogenicity consult review in DARRTS dated May 4, 2023). The classification as presented in [Table 86](#) was used to assess the ADA status. This same classification was also implemented to assess the APA status. The following sections briefly presents the Applicant's results and conclusions followed by overall reviewer's assessment.

14.4.1. Incidence Rate of ADAs and APAs

In up to 12 weeks (84 days) of treatment in MG0010, 2.3% (2/86) and 9.3% (8/86) of subjects treated with zilucoplan were positive for treatment-emergent ADA and positive APA respectively ([Table 87](#) and [Table 88](#)). The ADA titers of the two study subjects who were treatment-emergent ADA positive while treated with zilucoplan were 133 and 212. Among these two subjects, the first ADA positive result occurred at week 4 and week 12. The APA titers of eight subjects who were treatment-emergent anti-PEG positive while treated with zilucoplan were low and close to the minimum required dilution. Among these subjects, for APA, there were two first occurrences in week 1, three first occurrences in week 4, and three first occurrences in week 12.

From study MG0011, the incidence rate of treatment-emergent ADA and APA positive status in zilucoplan/zilucoplan treatment group were 2.2% (2/81) and 9.9% (8/81) respectively and was similar that of MG0090 ([Table 87](#) and [Table 88](#)). The incidence rate of treatment-emergent ADA and APA positive status in subjects who switched from placebo to zilucoplan was 0% and 1.2% (1/84) respectively. The two subjects in MG0011 with treatment-emergent ADA positive status are the subjects from the parent study (MG0010) with occurrence at week 4 and week 12 mentioned above. Two subjects became treatment-emergent anti-PEG antibody positive during MG0011 (1 in each group – placebo/zilucoplan and zilucoplan/zilucoplan) and the APA titers were low and close to minimum required dilution in these two subjects. Among the 8 subjects with treatment-emergent APA positive status in the zilucoplan/zilucoplan treatment group, there were three first occurrences in week 12, 2 first occurrences each in week 1, and two first occurrences each in week 4, and one first occurrence in week 60. The subject with treatment-emergent anti-PEG antibody positive status in the placebo/zilucoplan treatment group had the first positive occurrence at week 72.

Table 86. ADA Classification

Classification	Classification label	Definition
1	Pre-ADA negative–treatment induced ADA negative	Study participants who were ADA negative at Baseline and ADA negative at all sampling points post-Baseline.
2	Pre-ADA negative–treatment induced ADA positive	Study participants who were ADA negative at Baseline and ADA positive at any sampling point post-Baseline. It also included study participants who had a missing pretreatment sample (either missing or insufficient volume) at Baseline with 1 or more ADA positive post-Baseline samples.
3	Pre-ADA positive–treatment reduced ADA	Study participants who were ADA positive at Baseline and ADA negative at all sampling points post-Baseline.
4	Pre-ADA positive–treatment unaffected ADA	Study participants who were ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Observation Period) with titer values of the same magnitude as Baseline (less than a predefined fold difference from the Baseline value, which was defined within the validation of the assay, ie, MSR of the assay).
5	Pre-ADA positive–treatment boosted ADA positive	Study participants who were ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Observation Period) with increased titer values compared to Baseline (greater than a predefined fold difference increase from Baseline value, which was defined within the validation of the assay ie, MSR of the assay).
6	Inconclusive	Study participants who had an ADA positive Baseline sample and some post-Baseline samples were missing, while other post-Baseline samples were ADA negative.
7	Treatment-emergent ADA positive	Combination of 2 and 5.
8	Pre-ADA positive	Combination of 3, 4, and 5.

ADA=antidrug antibody; MSR=minimum significant ratio

Source: Table 5-2 (Pg 39 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

Note. The classification as presented in [Table 86](#) was also implemented for the assessment of APA response and status**Table 87. ADA Response and Incidence Rates (Study # MG0010, # MG0011)**

ADA Category	MG0010		MG0011	
	Placebo N=88 n/Nsub (%)	Zilucoplan 0.3 mg/kg N=86 n/Nsub (%)	Placebo/Zilucoplan 0.3 mg/kg N=90 n/Nsub (%)	Zilucoplan 0.3 mg/kg N=92 n/Nsub (%)
Pre-ADA negative–treatment induced ADA negative	83/88 (94.3)	80/86 (93.0)	20/84 (23.8)	21/81 (25.9)
Pre-ADA negative–treatment induced ADA positive	2/88 (2.3)	2/86 (2.3)	0	2/81 (2.5)
Pre-ADA positive–treatment reduced ADA	0	1/86 (1.2)	0	0
Pre-ADA positive–treatment unaffected ADA	0		0	0
Pre-ADA positive–treatment boosted ADA positive	0		0	0
Inconclusive	0		0	1/81 (1.2)
Missing	3/88 (3.4)	3/86 (3.5)	64/84 (76.2)	57/81 (70.4)
Total treatment-emergent ADA positive	2/88 (2.3)	2/86 (2.3)	0	2/81 (2.5)
Total pre-ADA positive	0	1/86 (1.2)	0	0

Source: Table 5-3 (Pg 40 of 91) and Table 5-5 (pg 53 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity
Reviewer Generated Table

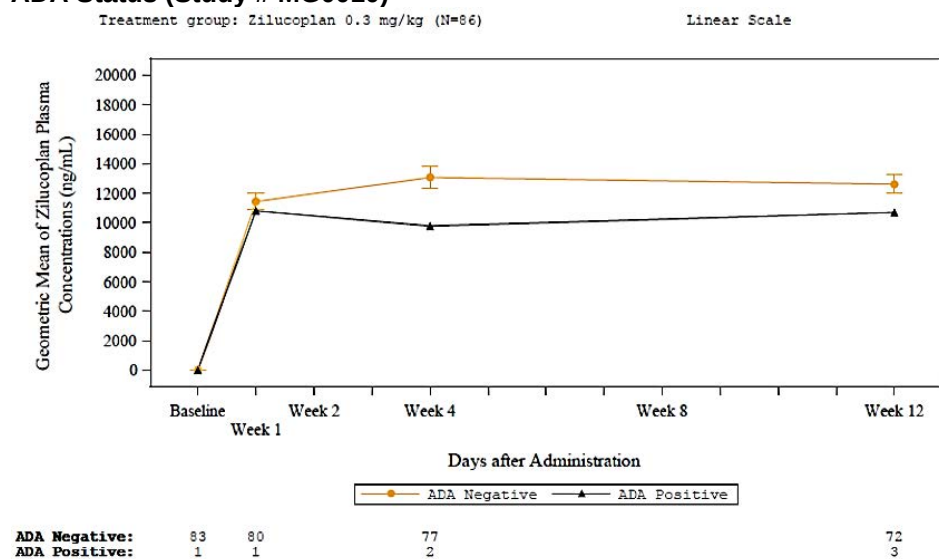
Table 88. APA Response and Incidence Rates (Study # MG0010, # MG0011)

APA Category	MG0010		MG0011	
	Placebo N=88 n/Nsub (%)	Zilucoplan 0.3 mg/kg N=86 n/Nsub (%)	Placebo/Zilucoplan 0.3 mg/kg N=90 n/Nsub (%)	Zilucoplan 0.3 mg/kg/ 0.3 mg/kg N=92 n/Nsub (%)
Pre-ADA negative–treatment induced ADA negative	74/88 (84.1)	71/86 (82.6)	18/84 (21.4) 18/81 (22.2)	18/84 (21.4) 18/81 (22.2)
Pre-ADA negative–treatment induced ADA positive	4/88 (4.5)	8/86 (9.3)	1/84 (1.2)	8/81 (9.9)
Pre-ADA positive–treatment reduced ADA	1/88 (1.1)	2/86 (2.3)	0	0
Pre-ADA positive–treatment unaffected ADA	4/88 (4.5)	2/86 (2.3)	1/84 (1.2)	2/81 (2.5)
Pre-ADA positive–treatment boosted ADA positive	2/88 (2.3)	0	0	0
Inconclusive	0	1/86 (1.2)	7/84 (8.3)	3/81 (3.7)
Missing	3/88 (3.4)	2/86 (2.3)	57/84 (67.9)	50/81 (61.7)
Total treatment-emergent ADA positive	6/88 (6.8)	8/86 (9.3)	1/84 (1.2)	8/81 (9.9)
Total pre-ADA positive	7/88 (8.0)	4/86 (4.7)	1/84 (1.2)	2/81 (2.5)

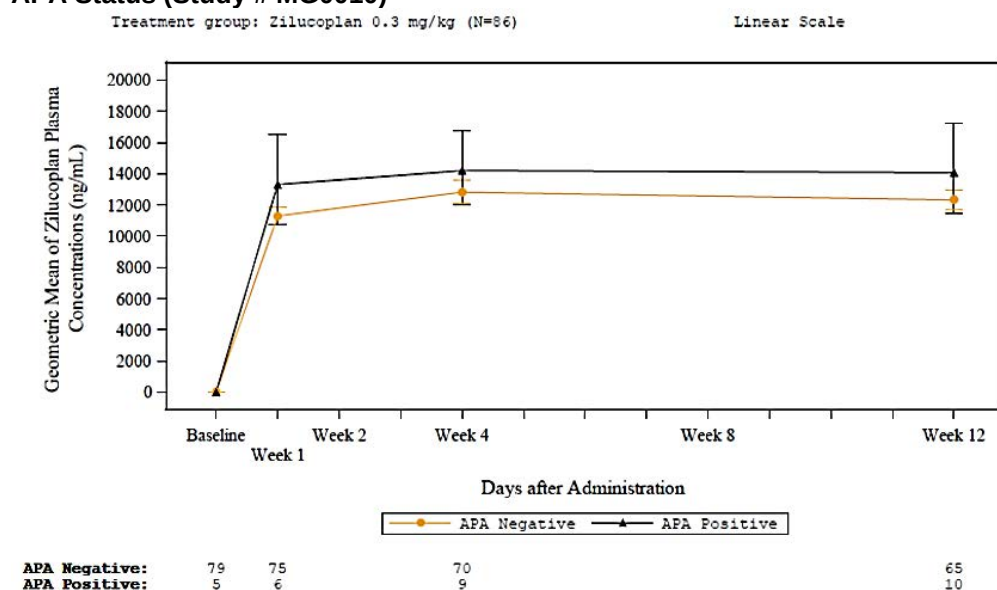
Source: Table 5-4 (Pg 46 of 91) and Table 5-6 (pg 59 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity
Reviewer Generated Table

14.4.2. Impact of ADAs and APAs on Zilucoplan PK

The Applicant concluded from [Figure 6](#) and [Figure 7](#) that ADA and APA status did not influence zilucoplan concentration. Specifically, the subjects who had treatment-emergent ADA/APA positive status had similar zilucoplan plasma concentrations compared with subjects with ADA/APA negative status. From the PK results of Study MG0011 the same above conclusion was made for the influence of ADA/APA status on zilucoplan PK (Figure 5-8 and Figure 5-11 of Integrated Summary of Immunogenicity, Module 5.3.5.3).

Figure 6. Zilucoplan Plasma Concentrations (Geometric Mean ($\pm$ 95% CI)) Over Time by Cumulative ADA Status (Study # MG0010)

Source: Figure 5-2 (Pg 43 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

Figure 7. Zilucoplan Plasma Concentrations (Geometric Mean ($\pm$ 95% CI)) Over Time by Cumulative APA Status (Study # MG0010)

Source: Figure 5-5 (Pg 49 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

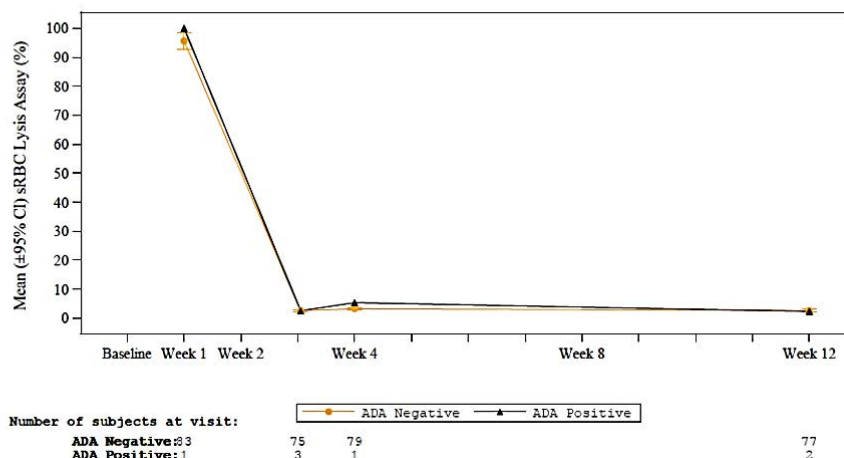
14.4.3. Impact of ADAs and APAs on Zilucoplan PD

The Applicant concluded from [Figure 8](#) and [Figure 9](#) that ADA and APA status did not influence the zilucoplan pharmacodynamic profile as measured by sRBC lysis. Specifically, there are no notable differences in the sRBC lysis for the subjects who had treatment-emergent ADA/APA positive status when compared with subjects with ADA/APA negative status. From the PD results of Study MG0011, the same above conclusion was made for the influence of ADA/APA

status on sRBC lysis by zilucoplan (Figure 5-9 and Figure 5-12 of Integrated Summary of Immunogenicity, Module 5.3.5.3)

Figure 8. Mean sRBC Lysis ($\pm 95\%$ CI) Over Time by Cumulative ADA Status (Study # MG0010)

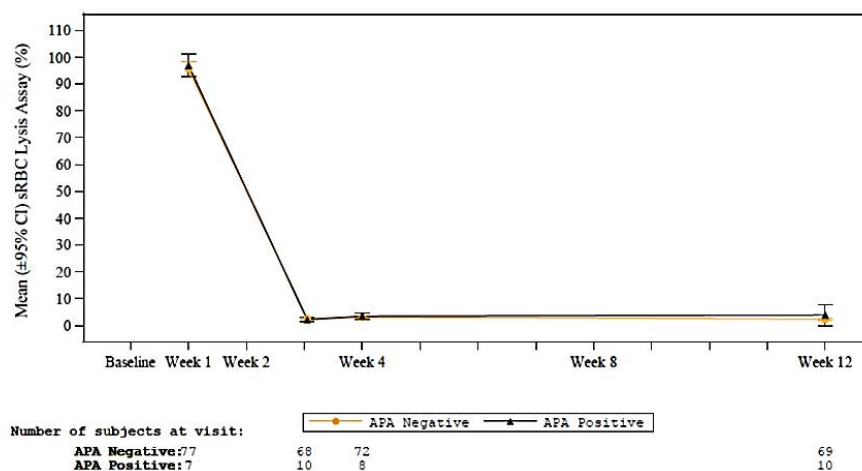
Treatment group: Zilucoplan 0.3 mg/kg (N=85)



Source: Figure 5-3 (Pg 44 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

Figure 9. Mean sRBC Lysis ($\pm 95\%$ CI) Over Time by Cumulative APA Status (Study # MG0010)

Treatment group: Zilucoplan 0.3 mg/kg (N=85)



Source: Figure 5-6 (Pg 50 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

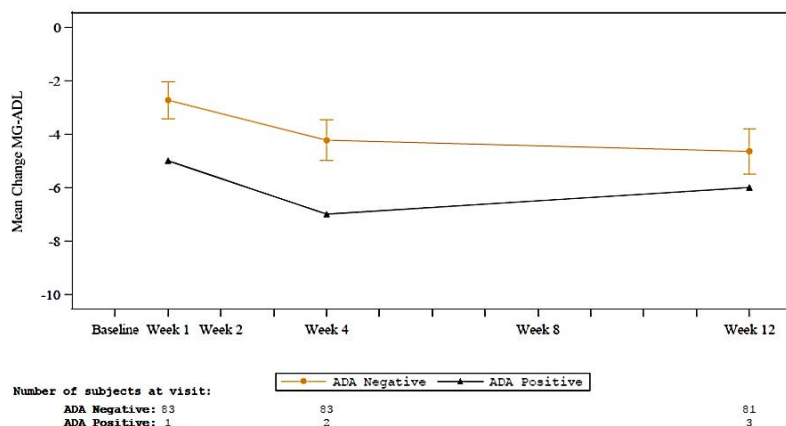
14.4.4. Impact of ADAs and APAs on Zilucoplan Efficacy

Based on [Figure 10](#), the Applicant concluded that the change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score was numerically greater in treatment-emergent ADA positive subjects compared with the subjects who were ADA negative. Among the 7 and 6 subjects who were treatment-emergent APA positive in zilucoplan ([Figure 11](#)) and placebo treatment groups respectively, four subjects in each had at least a 3-point reduction in MG-ADL score from baseline by Week 12. The Applicant concluded that given the large variability in MG-ADL scores and the small sample size of subjects who were APA positive, no conclusion

can be drawn about the effect of APA status on MG-ADL score. From study MG0011, the Applicant concluded that change from baseline in MG-ADL score was similar in ADA/APA positive and negative subjects (Figures 5-7 and 5-10 of Integrated Summary of Immunogenicity, Module 5.3.5.3).

Figure 10. Mean ($\pm$ 95% CI) Change From Baseline in MG-ADL Total Score Over Time by Cumulative ADA Status

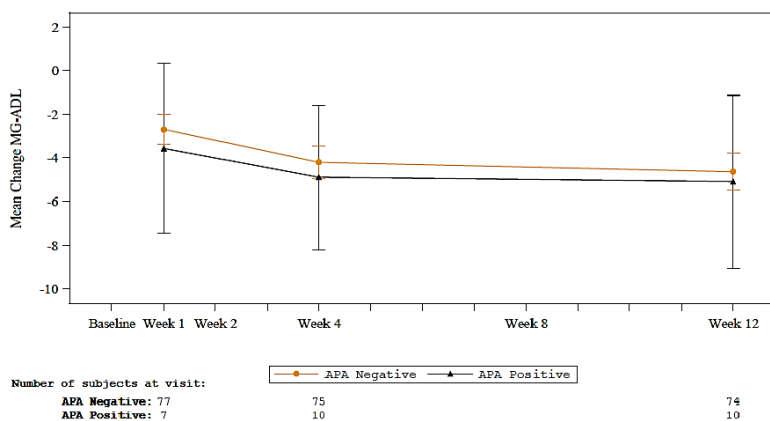
Treatment group: Zilucoplan 0.3 mg/kg (N=86)



Source: Figure 5-1 (Pg 42 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

Figure 11. Mean ($\pm$ 95% CI) Change From Baseline in MG-ADL Total Score Over Time by Cumulative APA Status

Treatment group: Zilucoplan 0.3 mg/kg (N=86)



Source: Figure 5-4 (Pg 48 of 91) from Module 5.3.5.3 Integrated Summary of Immunogenicity

14.4.5. Impact of ADAs and APAs on Zilucoplan Safety

The Applicant concluded that ADA and APA status do not appear to affect safety of zilucoplan. In Study MG0010, one treatment-emergent adverse event (TEAE - arrhythmia) was reported in one of two subjects starting on or after the first treatment-emergent ADA positive result in zilucoplan group. Of the two subjects who were treatment-emergent ADA positive in the placebo treatment group, no TEAEs were reported starting on or after the first treatment-emergent ADA

positive result was reported. No TEAEs of autoimmune disorders, hypersensitivity reactions, or injection site reactions were reported in subjects on or after treatment-emergent ADA positive status in either treatment group.

In 3 of 8 subjects with treatment-emergent APA positive status in zilucoplan group, 4 of 32 TEAEs were hypersensitivity reactions or injection site reactions with no TEAE in autoimmune disorders. In three of six subjects with treatment-emergent APA positive status in placebo group, nine TEAEs starting on or after the first treatment-emergent APA positive result were reported with none of them related to hypersensitivity reactions, injection site reactions, or autoimmune disorders. A similar safety observation as a function of ADA/APA status were made in Study MG0011. The proportion of subjects with TEAEs as a function of ADA/APA status does not appear to be different in zilucoplan and placebo group.

Reviewer's Assessment: Overall, based on the above summary, the occurrence of antidrug and anti-PEG antibodies is low. The available data are too limited to make definitive conclusions regarding immunogenicity and its impact on pharmacokinetics, pharmacodynamics, safety, or efficacy of zilucoplan.

14.5. Pharmacometrics Assessment

14.5.1. Applicant's Analysis

Population PK Analysis

The adult population pharmacokinetic (popPK) was developed using a dataset of 2,174 evaluable plasma concentrations from 200 subjects who received zilucoplan. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in nonlinear mixed-effects modeling (NONMEM), version 7.5 (ICON, Maryland) was used for the popPK analysis. An overview of the studies with available data are provided in [Table 89](#).

Table 89. Summary of Study Designs With Zilucoplan Used in the Current Analysis

Study number	Type	Subject numbers: total/active population	Treatment regimen
RA101495-1001/UP0112 (First in human)	Adult, HV, Phase 1	28/18	SAD: single SC doses of placebo, 0.05, 0.1, 0.2, and 0.4 mg/kg zilucoplan MD: 0.2 mg/kg zilucoplan once daily SC for 7 days
RA101495-01.102/UP0113 (Ethnic bridging)	Adult, HV, Phase 1	36/30	SD cohort: single SC doses of placebo, 0.1, and 0.3 mg/kg RA101495 MD cohort: daily SC injections of placebo, and 0.3 mg/kg for 14 days
RA101495-02.201/MG0009 (gMG, main portion)	Adult, gMG patients, Phase 2	44/32	Placebo, 0.1 mg/kg or 0.3 mg/kg SC zilucoplan once daily
RA101495-03.101/UP0114 (renally impaired function)	Adult, HV, Phase 1	8/8	0.3 mg/kg SC zilucoplan single dose (HV only)
RA101495-02.101/UP0093 (thorough QT)	Adult, HV, Phase 1	64/28	0.6mg/kg zilucoplan once daily SC for 7 days/Placebo/Moxifloxacin
RA101495-02.301/MG0010 (RAISE)	Adult, gMG patients, Phase 3	156/78 [#]	Daily SC doses of 0.3 mg/kg zilucoplan or placebo. Screening Period of up to 4 weeks and a 12- week Treatment Period. PK and efficacy assessments at screening (efficacy only), day 1 (baseline), day 8 (week 1), day 15 (week 2), day 29 (week 4), day 57 (week 8), and day 84 (week 12, end of study).

[#]as planned in protocol

gMG: general Myasthenia Gravis, HV: healthy volunteer, MD: multiple dose, SAD: single ascending dose, SC: subcutaneous, SD: single dose.

Source: The Applicant's PopPK report cI0508-rep-2109-ucb, Page 18, Table 1

The popPK modeling population had a range of body weights from 47.6 kg to 171 kg and ages ranging from 20 to 76 years. The majority of the subjects were female (58.6%) and white (68%). In total, 203 subjects were included in the analysis, consisting of 86 healthy volunteers (42.4%) and 117 subjects with gMG (57.6%) ([Table 90](#)).

Table 90. Baseline Characteristics of Zilucoplan PK Population in Study

Covariate	UP0112 (FIH)	MG0009 (gMG)	UP0093 (tQT)	UP0114 (HV/RF)	UP0113 (Bridging)	MG0010 (RAISE)	Total
Age (years)	28.7 (12.6) 24.0 [20.0/65.0] [18/0]	49.3 (16.0) 55.0 [20.0/76.0] [30/0]	38.5 (11.2) 40.0 [20.0/55.0] [32/0]	55.4 (6.67) 56.5 [46.0/63.0] [8/0]	47.1 (11.2) 47.0 [21.0/64.0] [28/0]	52.6 (14.8) 55.0 [20.0/75.0] [87/0]	47.1 (15.5) 49.0 [20.0/76.0] [203/0]
Weight (kg)	67.0 (12.5) 62.2 [50.9/91.0] [18/0]	101 (28.7) 94.0 [58.0/171] [30/0]	74.9 (12.7) 77.1 [51.4/94.4] [32/0]	77.3 (6.48) 76.0 [67.8/88.0] [8/0]	65.2 (9.59) 64.5 [47.6/87.7] [28/0]	90.1 (22.9) 86.3 [49.6/145] [87/0]	83.3 (23.3) 79.4 [47.6/171] [203/0]
Sex							
Male	2 (11.1%)	17 (56.7%)	15 (46.9%)	4 (50.0%)	11 (39.3%)	35 (40.2%)	84 (41.4%)
Female	16 (88.9%)	13 (43.3%)	17 (53.1%)	4 (50.0%)	17 (60.7%)	52 (59.8%)	119 (58.6%)
Race							
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (8.0%)	7 (3.4%)
W	13 (72.2%)	25 (83.3%)	11 (34.4%)	8 (100.0%)	14 (50.0%)	67 (77.0%)	138 (68.0%)
B/AA	1 (5.6%)	4 (13.3%)	21 (65.6%)	0 (0.0%)	0 (0.0%)	6 (6.9%)	32 (15.8%)
A	3 (16.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (8.0%)	11 (5.4%)
J	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (50.0%)	0 (0.0%)	14 (6.9%)
O	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Population							
HV	18 (100.0%)	0 (0.0%)	32 (100.0%)	8 (100.0%)	28 (100.0%)	0 (0.0%)	86 (42.4%)
gMG	0 (0.0%)	30 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	87 (100.0%)	117 (57.6%)

Continuous values are shown as mean (standard deviation) median [range] [sample size/number missing]. Values were rounded to 3 significant digits. Categorical values are shown as number of subjects (%). W = White, B/AA = Black / African American, A = Asian, J = Japanese, AI/AN = American Indian or Alaska Native, O = Other, HV = healthy volunteer, gMG = general Myasthenia Gravis patient

Source: The Applicant's PopPK report, Page 30, Table 2

PopPK Model

A 2-compartment model with first order absorption, followed by a target-mediated exposure enhancement model, without incorporating total complement component 5 (C5) concentration. The model was implemented using the quasi-steady-state approximation to the target-mediated drug disposition equations that solely relied on total zilucoplan concentration. Allometric coefficients were estimated to account for 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).

The target-mediated exposure enhancement model was evaluated, and a covariate analysis was performed to determine the potential impact of covariate on CL and maximum target density (Rmax).

Covariate Analysis

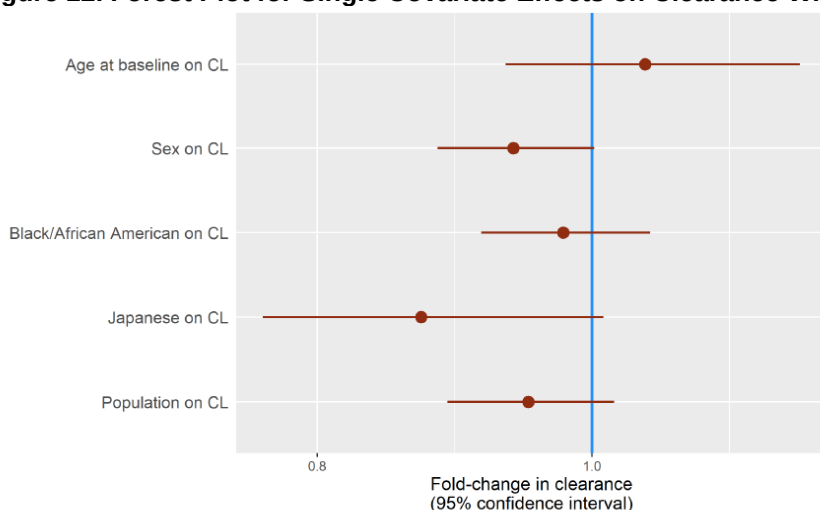
A covariate analysis was performed to assess the potential effect of different demographic covariates on CL and Rmax. The following covariates were tested:

- Body weight at baseline (included as a priori for PK)
- Age at baseline
- Sex
- Race
- Population (healthy subjects versus subjects with gMG)

Based on the decrease in objective function value, effect of race on Rmax (with race categories Black/African Americans, Japanese, and all others) was the only significant covariate at the $p < 0.05$ level. Since the CIs of the effect of race on Rmax for both Black/African Americans versus all others, and for Japanese versus all others included 1 (indicating no statistical significance at $p = 0.05$, as shown in [Figure 12](#) and [Figure 13](#)), the relevant race categories were not considered significant and thus not included in the model.

Furthermore, the analysis demonstrated no significant association between race and overall exposure at the dose of 0.3 mg/kg, nor any effect on average steady state concentration at this dose. Consequently, the base model without covariates was considered as the final model.

Figure 12. Forest Plot for Single Covariate Effects on Clearance With 95% CIs

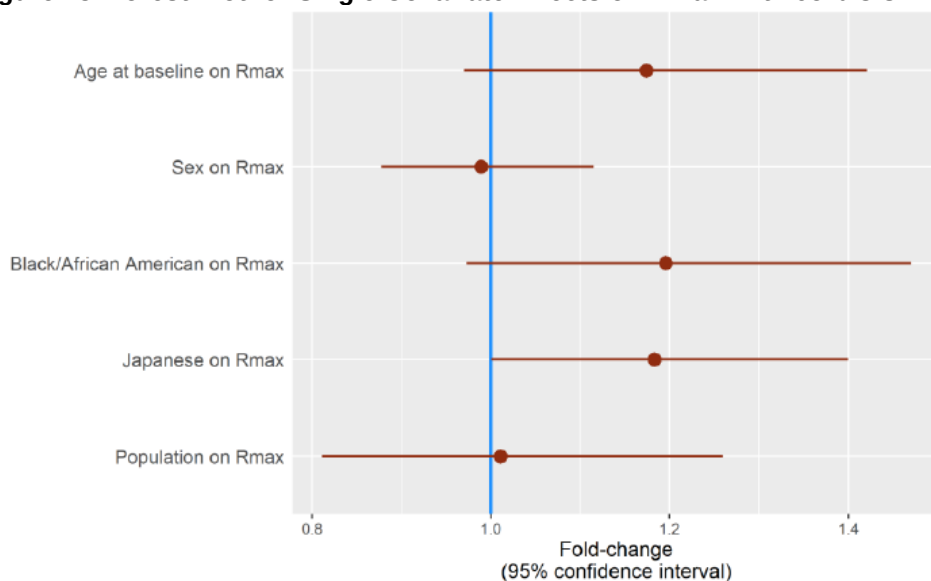


CI=confidence interval; CL=clearance; gMG=generalized myasthenia gravis

Sex=females relative to males; Race=Black/African Americans and Japanese relative to all others;

Population=participants with gMG relative to healthy volunteers. Continuous covariate age is scaled to estimate the fold change across 95% of the covariate range

Source: The Applicant's popPK report, Page 44, Figure 13

Figure 13. Forest Plot for Single Covariate Effects on Rmax With 95% CIs

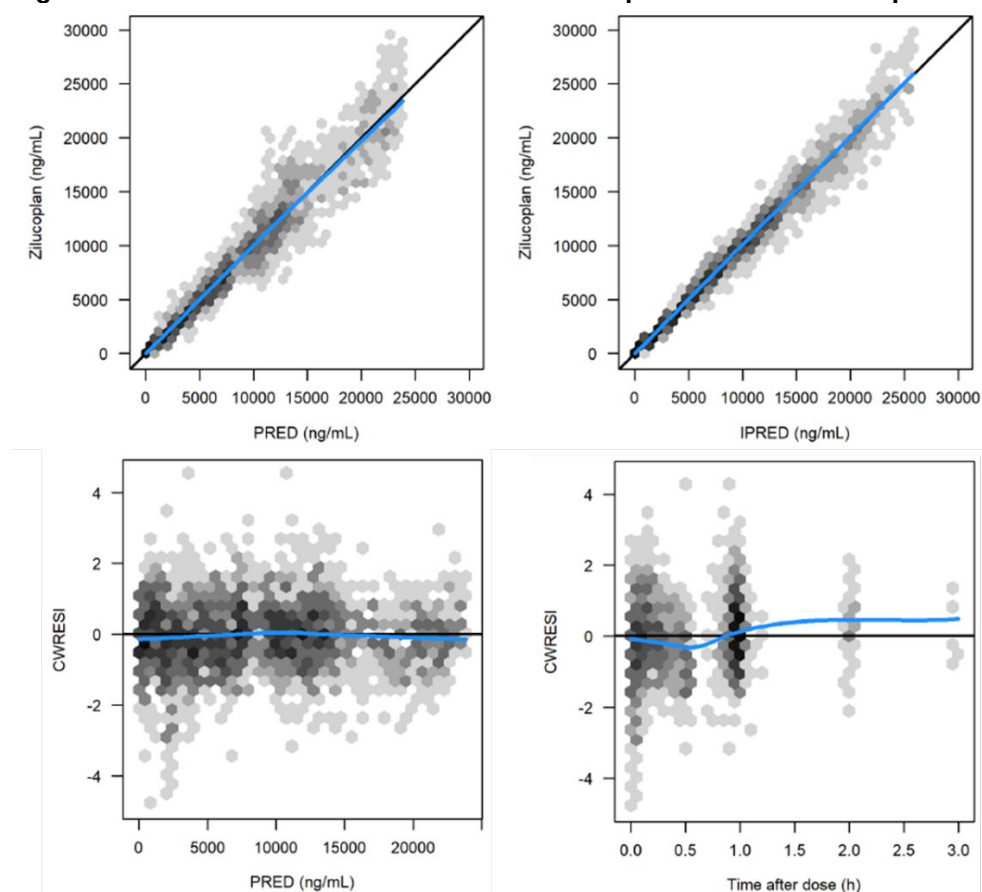
CI=confidence interval; gMG=generalized myasthenia gravis; Rmax=maximum target density

Sex=females relative to males; Race=Black/African Americans and Asian/Japanese relative to all others;

Population=participants with gMG relative to healthy volunteers. Continuous covariate age is scaled to estimate the fold change across 95% of the covariate range

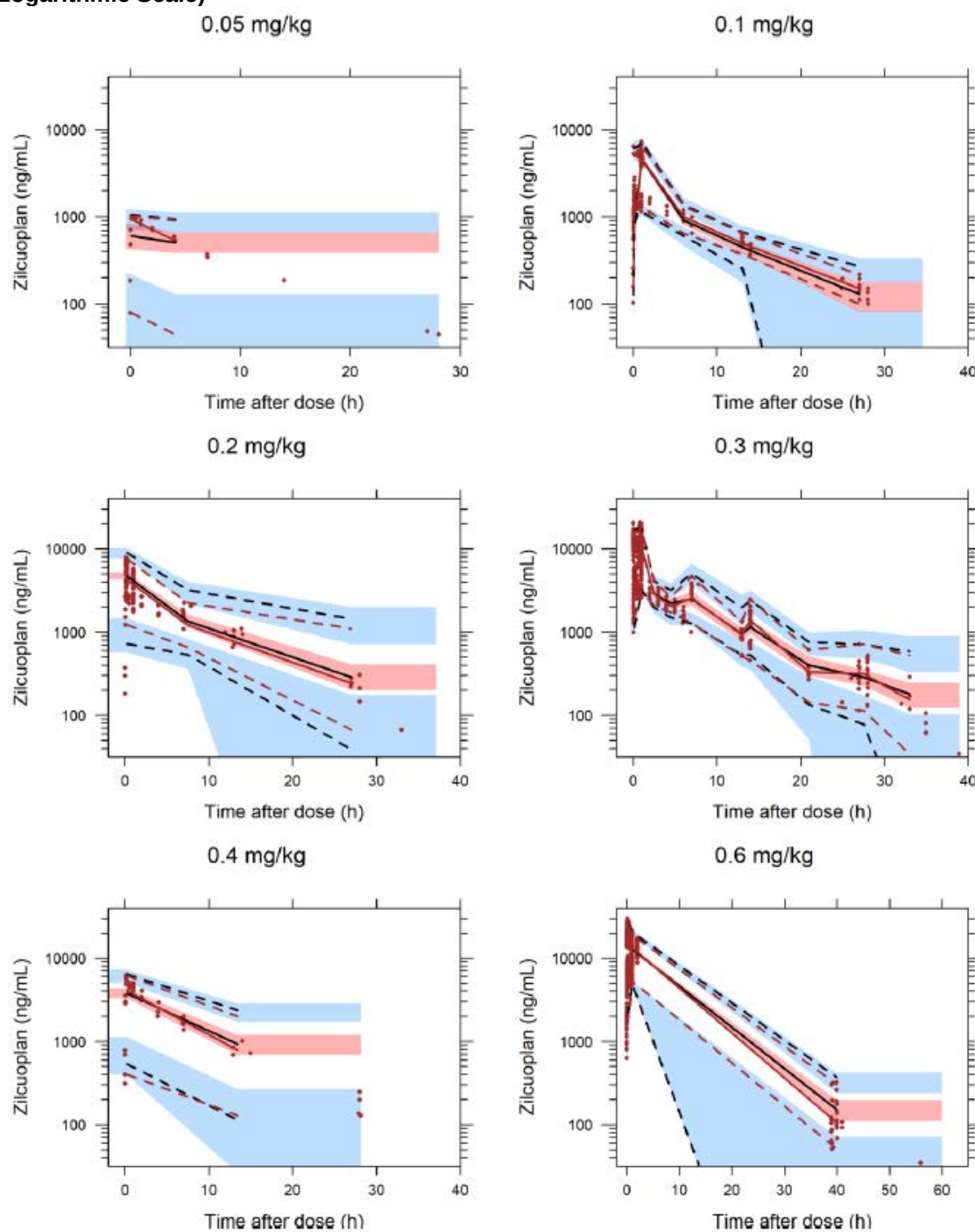
Source: The Applicant's popPK report, Page 44, Figure 14

The final popPK model for zilucoplan was assessed with diagnostics plots including goodness-of-fit ([Figure 14](#)) and pcVPC ([Figure 15](#)).

Figure 14. Goodness-of-Fit Plots for the Final PopPK Model for Zilucoplan

Source: The Applicant's popPK report, Page 47-49, Figure 16, Figure 17 and Figure 18

The black lines are zero lines, the blue lines are loess smoothers through the data. The darkness of the hexagons corresponds to the data density at that location.

Figure 15. pVPCs for Zilucoplan Stratified by Dose Using the Final PopPK Model (run110, Logarithmic Scale)

Source: The Applicant's popPK report, Page 51, Figure 20

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

Parameter estimates from the final popPK model are presented in [Table 91](#).

For a typical subject with a body weight of 70 kg, the estimated pharmacokinetic parameters were as follows: CL was 0.0845 L/hr, Vc was 3.51 L, Vp was 3.45 L, Q was 0.566 L/hr, absorption rate constant (ka) was 1.22/hr, internalization rate constant (kint) was 0.00320/hr, quasi-stationary constant (Kss) was 63.3 ng/mL, and maximum target density (Rmax) was 1780 ng/mL. The allometric exponent for body weight (WT) on CL and Q were estimated to be 0.715 and 0.452, respectively. The slope of the logarithm of ka on WT was estimated to be -1.01. Interindividual variability was observed in CL (16.8%), Vc (15.7%), Q (39.4%), ka (41.5%), and Rmax (21.5%).

The estimates of proportional and additive residual variance were deemed acceptable, with values of 9.26% and 63.3%, respectively. This indicates that the popPK model can adequately characterize the interindividual variability of these parameters ([Table 91](#)).

Table 91. Final PopPK Model: Zilucoplan Parameter Estimates

Parameter	NONMEM Estimate (95% CI)	NONMEM IIV	SIR Estimate (95% CI)	SIR IIV
ka (1/h)	1.22 (0.809/1.85)	41.5%	1.22 (0.939/1.66)	41.7%
CL (L/h)	0.0845 (0.0815/0.0875)	16.8%	0.0845 (0.0817/0.0877)	16.8%
Vc (L)	3.51 (3.31/3.71)	15.7%	3.51 (3.33/3.72)	15.8%
Q (L/h)	0.566 (0.494/0.638)	39.4%	0.567 (0.488/0.647)	39.6%
Vp (L)	3.45 (3.19/3.72)		3.45 (3.17/3.75)	
Kss (ng/mL)	63.3 (13.4/113)		62.4 (33.0/107)	
Kint (1/h)	0.00320 (0.00262/0.00379)		0.00321 (0.00275/0.00363)	
Rmax (ng/mL)	1780 (1610/1960)	21.5%	1780 (1630/1980)	21.8%
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)	
Additive RUV (ng/mL)	63.3 (16.5/110)		64.0 (46.6/87.9)	

ka: absorption rate constant, CL: clearance, Vc: central volume, Q: intercompartmental CL, Vp: peripheral volume of distribution, Kss: quasi-stationary constant, Kint: internalization rate constant, Rmax: maximum target density, RUV: residual unexplained variability

Source: The Applicant's popPK report, Page 54, Table 10

PK Simulations

The impact of the three administered dose categories in the MG0010 study on exposure measures was examined based on body weight. The final popPK model estimates were utilized to generate pharmacokinetic empirical bayes estimates for all records in the National Health and Nutrition Examination Survey (NHANES) database, utilizing the dosing regimen of the MG0010 study:

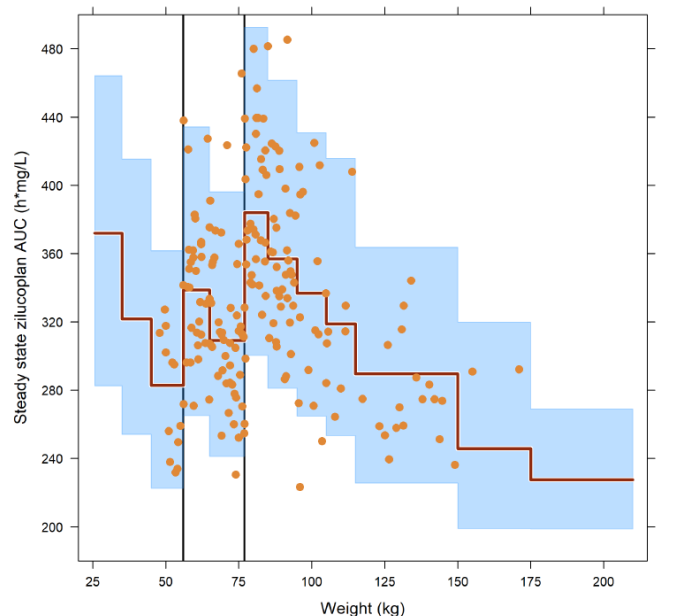
- 16.6 mg per day for weight <56 kg
- 23.0 mg per day for weight ≥56 kg and <77 kg
- 32.4 mg per day for weight ≥77 kg

The resulting exposure measures at steady state were used to derive the median and 90% of the simulated exposure measures, and these were compared with the simulated exposure measures

for all subjects in the popPK analysis. These results were graphically compared for the impact of body weight ([Figure 16](#)).

Overall, the results show that the simulated exposures are consistent across weight ranges of 25 kg to over 150 kg for all three dosing categories. These findings suggest that the intended dosing regimen adequately accounts for the influence of body weight on exposure to zilucoplan.

Figure 16. Distribution of Steady State Zilucoplan AUC by Weight Using the Final PopPK Model



popPK=population pharmacokinetic; ZLP=zilucoplan
Red line and blue area=median and 90% of simulated values for patients sampled from the Nihans database. Orange circles=individual predicted values; vertical black lines=weights (56kg and 77kg) where dose changes from 16.6mg to 23mg to 32.4mg

Source: The Applicant's popPK report, Page 165, Figure 88

Reviewer's Comments: Overall, the Applicant's popPK model can adequately characterize the PK profiles of zilucoplan in patients with gMG. The reviewer concurs with the ADME parameters presented by the Applicant in the proposed label.

14.5.2. Reviewer's Analysis

Data Sets

Data sets used are listed in [Table 92](#).

Table 92. Analysis Data Sets

Study	Name	Link to EDR
UP0112	zil_220407_xpt.xpt	\\CDSESUB1\EVSPROD\nda216834\0001\m5\datasets\cl0508\analysis\legacy\datasets\
UP0113	zilcav_220523_xpt.xpt	
MG0009		
UP0114		
UP0093		
MG0010		

Software

PopPK model fitting was performed in NONMEM 7.5.0 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.0.

Results

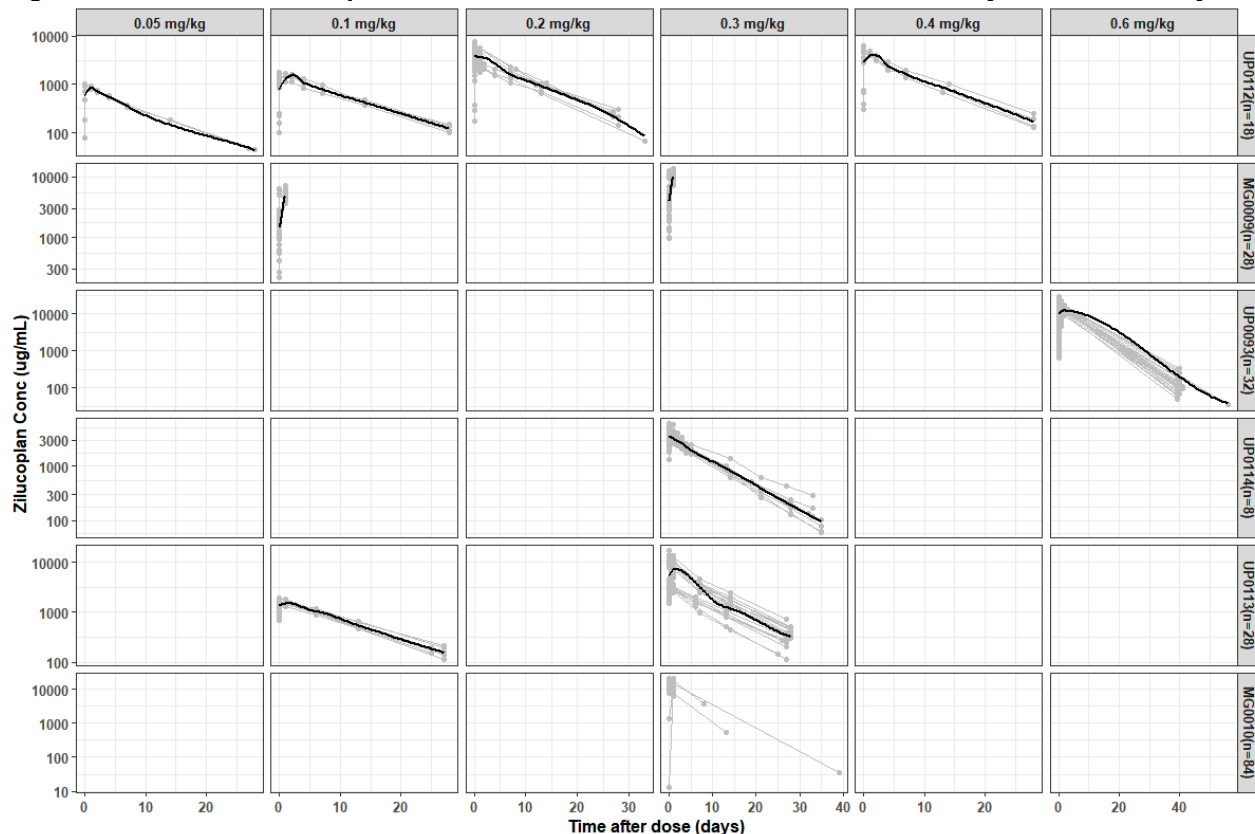
The reviewer was able to replicate the Applicant's popPK results with NONMEM (version:7.5.0). The Applicant's popPK analysis is adequate for characterizing the PK profiles for zilucoplan.

Overview of Observed Data

The PK profiles of zilucoplan in gMG subjects who received a weight-based dose are illustrated in [Figure 17](#).

The reviewer performed an independent analysis using the final popPK model submitted by the Applicant to assess the accuracy of the labeling statement regarding distribution, biotransformation, and elimination parameters after subcutaneous administration of zilucoplan in adult subjects with gMG.

Figure 17. Observed Zilucoplan Concentration Versus Time After First Dose by Dose and Study



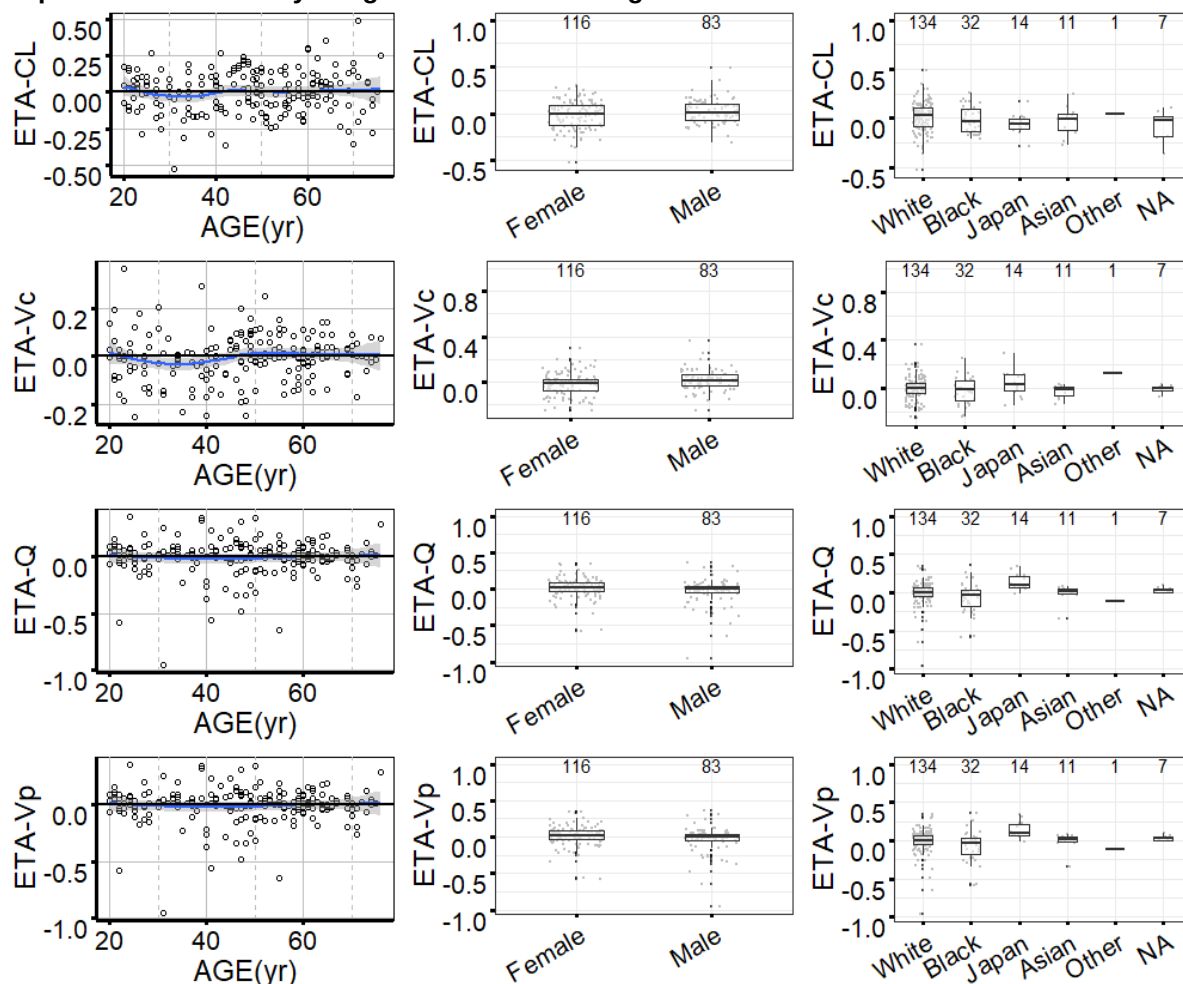
Source: Reviewer's analysis

Note: Observed values are indicated by solid grey circles, the grey solid lines represent the observed medians. The black solid lines are loess smoothers through the data.

Graphical analyses were conducted by the reviewer to confirm the Applicant's finding. There is no clear trend indicating a correlation between age, sex, race, and the clearance or volume of distribution with bodyweight allometric scaling ([Figure 18](#)).

This is consistent with labeling statement proposed by the Applicant that popPK analysis evaluating the influence of age, sex, and race did not reveal any clinically significant impact of these factors on zilucoplan exposures.

Figure 18. Random Effects on Clearance and Volume of Distribution vs. Age, Sex and Race for PopPK Model With Only Weight Allometric Scaling



Source: Reviewer's analysis

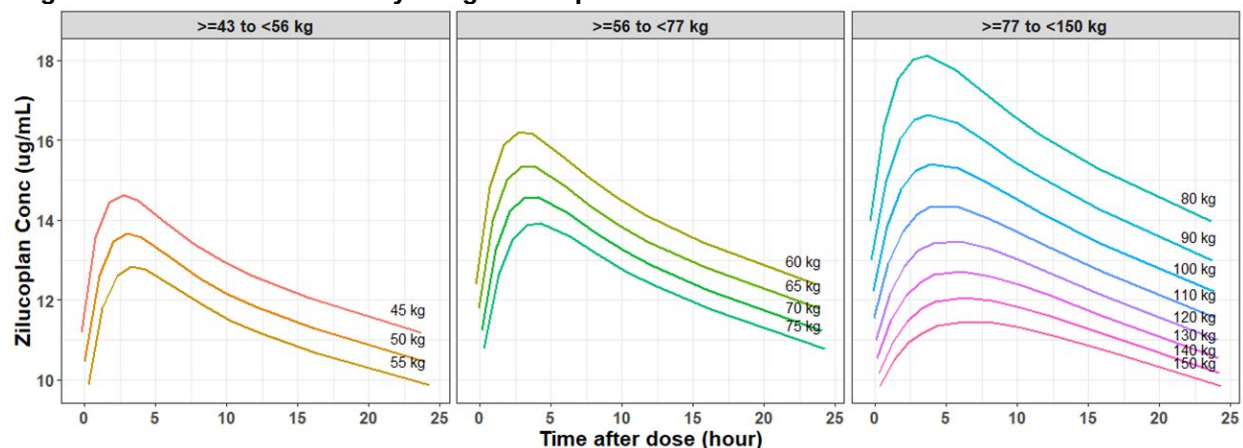
In addition, the reviewer conducted simulations on subjects with typical weights for each body weight groups ([Figure 19](#) and [Figure 20](#)). By assessing the impact of weight on PK parameters within different weight groups, the reviewer confirmed the Applicant's finding that body weight is a significant covariate.

Furthermore, the reviewer conducted an analysis by plotting the change of MG-ADL scores against visits within each body weight group in Study MG0010 to assess the appropriateness of the body weight-based regimen. Despite the limited sample size in the lower body weight group

(i.e., ≥ 43 to < 56 kg), the findings demonstrated no significant differences in the change of MG-ADL scores from baseline across the various body weight groups.

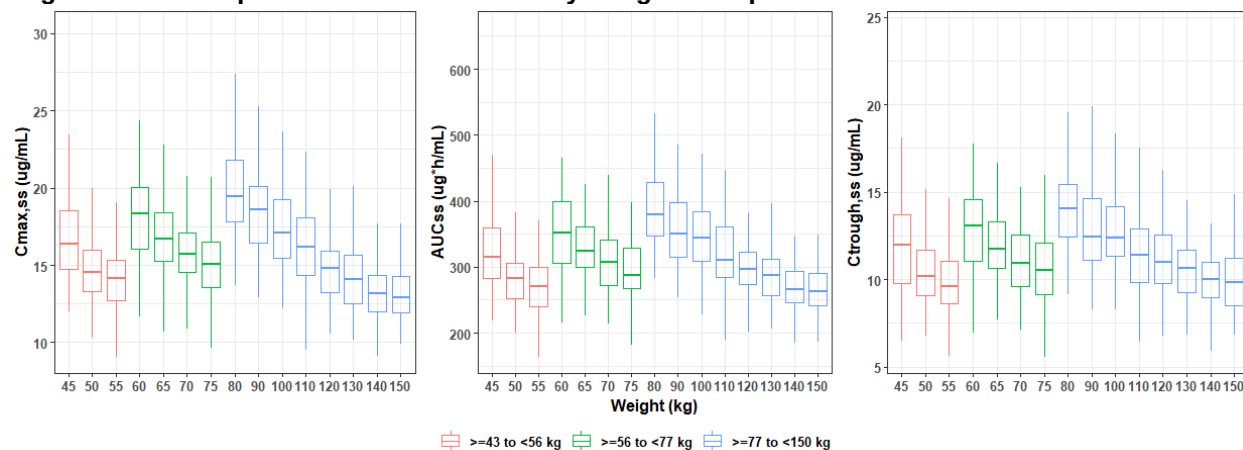
These results suggest that the body weight-based regimen is a reasonable approach, despite potential variations in PK exposure (simulated steady-state AUC ranging from 200 to 500 $\mu\text{g}\cdot\text{h}/\text{mL}$) associated with body weight. The analysis consistently showed comparable efficacy outcomes across different body weight categories ([Figure 21](#)), providing support for the use of a dosing regimen based on body weight.

Figure 19. Simulated Steady State PK Profiles of Zilucoplan for the Proposed Weight-Based Dose Regimen Across Different Body Weight Groups



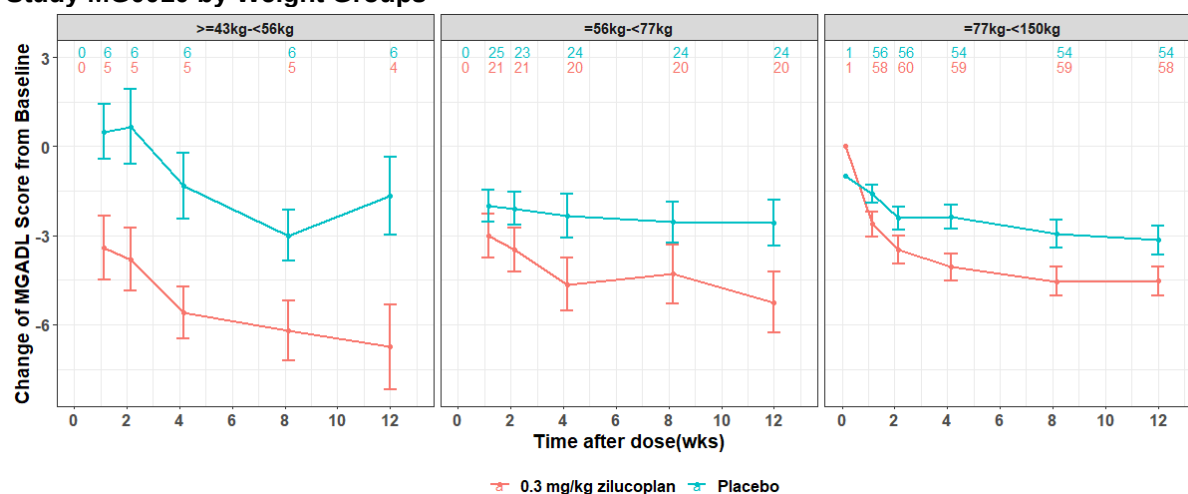
Source: Reviewer's analysis

Figure 20. Simulated PK Exposure at Steady State Following Daily Proposed Weight-Based Dose Regimen of Zilucoplan Across Different Body Weight Groups



Source: Reviewer's analysis

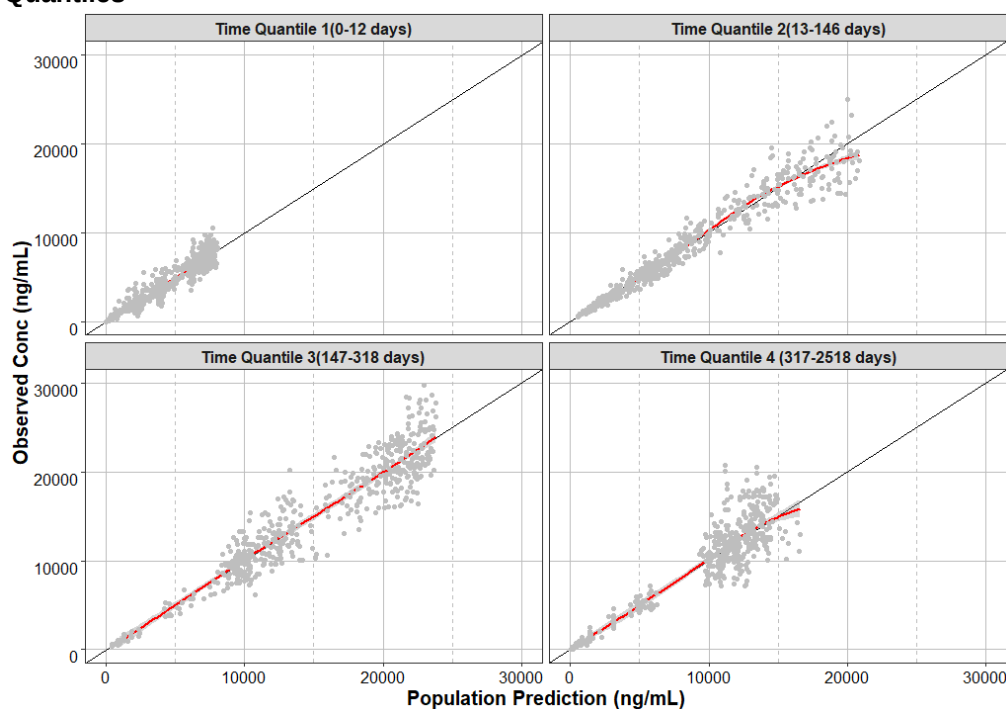
Figure 21. Mean (95%CI) of MG-ADL Score Change From Baseline by Time After Dose (mITT) From Study MG0010 by Weight Groups



Source: Reviewer's analysis

Evaluation of Labeling Statement

The Applicant stated in the proposed label: “The population PK analysis showed that zilucoplan PK was not ^{(b) (4)} time dependent.” The reviewer generated a plot ([Figure 22](#)) showing the relationship between observed concentration and population prediction for zilucoplan across time quantiles in PK dataset, which suggests that the zilucoplan PK is not time dependent. For further information on dose dependency and proportionality, please refer to the review provided by the clinical pharmacology reviewer.

Figure 22. Relationship Between Observed Concentration and Population Prediction Across Time Quantiles

Source: Reviewer's analysis

Table 93. Listing of Analyses Codes and Output Files

File Name	Description	Location
Pk_analysis_Zilucoplan.R	PK and PopPK analysis file	\\Review\2022\NDA 216834 Zilucoplan\PopPK\Rscript

14.6. Pharmacogenetics

Not Applicable

15. Study / Trial Design

15.1. Study MG0009

This study was a dose-finding study and is not included in the proposed labeling. Its design and population were very similar to study MG0010. The primary endpoint of change from baseline on the QMG was not statistically significant. QMG and MG-ADL (key secondary endpoint) scores had mean changes over 12 weeks that were higher in the zilucoplan groups than placebo (-6.0 versus -3.2 for QMG; and -3.4 versus -1.1 for MG-ADL). Data from this study informed the safety review and the clinical pharmacology review.

15.1.1. Design, Study MG0009

Study MG0009 was a two-part, multicenter, dose-ranging study in 44 subjects to evaluate the safety, tolerability, and preliminary efficacy of once daily subcutaneous zilucoplan. Subjects were randomly assigned (1:1:1) to 12 weeks of placebo (n=15), zilucoplan 0.1 mg/kg (n=15), or zilucoplan 0.3 mg/kg (n=14) after stratification by screening QMG score. Subjects were expected to remain on stable doses of all other medications for MG unless otherwise medically indicated.

The open-label portion of study MG0009 consisted of 42 subjects from the placebo-controlled period, who did not have study drug permanently discontinued. Subjects on the 0.3 mg/kg dose in the placebo-controlled portion continued on 0.3 mg/kg in the open-label extension; subjects on 0.1 mg/kg continued on 0.1 mg/kg; and subjects on placebo were randomized (1:1) to 0.1 mg/kg or 0.3 mg/kg. However, during the OL phase of this study, all subjects were changed to the zilucoplan 0.3 mg/kg dose pursuant to a protocol amendment.

15.1.2. Eligibility Criteria, Study MG0009

The eligibility criteria for Study MG0009 were the same as for Study MG0010, except that MG0009 did not set a minimum MG-ADL score for enrollment. However, subjects in MG0009 and MG0010 had similar mean screening MG-ADL and QMG scores.

The main eligibility criteria for the open-label extension of study MG0009 were completion of the placebo-controlled period without permanent discontinuation of zilucoplan.

15.1.3. Statistical Analysis Plan, Study MG0009

The primary efficacy endpoint was the change from baseline (CFB) to week 12 in the QMG score. The key secondary efficacy endpoints were:

- Change from baseline to week 12 in the MG-ADL total score
- Change from baseline to week 12 in the MGC total score
- Change from baseline to week 12 in the MG-QOL15r Survey
- The number of subjects receiving rescue therapy over 12 weeks
- The number of subjects with MG-ADL total of 0 or 1 at week 12
- The number of subjects achieving 3-point or greater reduction in QMG at week 12

15.1.4. Demographics, Study MG0009

The majority of subjects enrolled in MG0009 completed the study, and most completers entered the extension study.

Subjects were balanced demographically, including by sex. Subjects resembled the wider MG population (mean age 50 years, 16% >65 years, BMI 33 kg/m², 80% white) and were balanced between groups.

The two groups were generally balanced in terms of comorbidities (43% had previous/ongoing psychiatric SOC; 28% previous/ongoing infectious SOC.). Commonly reported comorbid medical conditions by PT were hypertension (52%), depression (27%), and diabetes (18%). Sleep apnea was one PT that was imbalanced (13.3% in PLO and low dose zilucoplan, 57% in high dose zilucoplan), though it is unlikely to have introduced a type 1 error.

Baseline myasthenia characteristics were balanced between groups and similar to MG0010 (mean age at disease onset of 41 years, mean disease duration 8.4 years, median MG-ADL 7, median QMG 18, 98% were on concomitant MG medications [91% on cholinesterase inhibitors, 91% on steroids, 61% on immunoglobulin]).

16. Efficacy

Not Applicable.

17. Clinical Safety

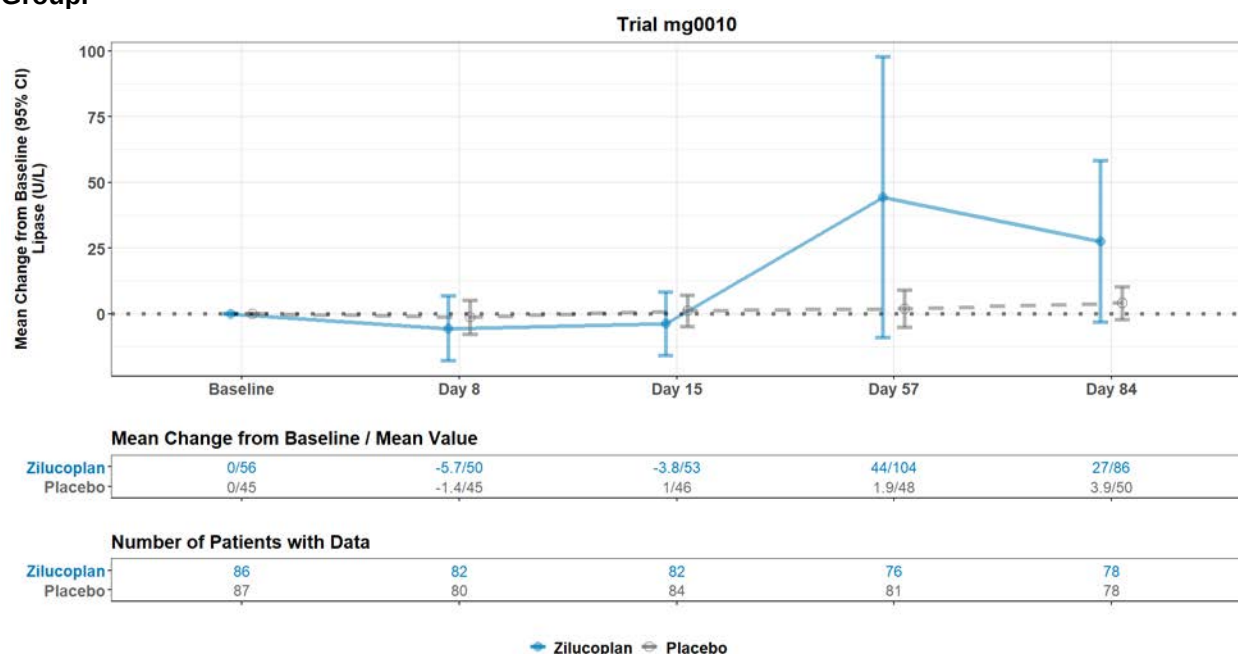
17.1. QT Prolongation

No significant QTcF prolongation effect of zilucoplan has been identified.

The effect of zilucoplan was evaluated in study # UP0093, which was a Phase 1, double-blind, randomized, placebo- and active-controlled, multiple-dose, single-center, parallel group with nested crossover study of the effects of suprathreshold dose of zilucoplan on cardiac repolarization in healthy adult study participants. The highest dose evaluated was 0.6 mg/kg, which covered the anticipated high clinical exposure in study UP0093. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that zilucoplan is associated with significant QTc prolonging effects. Findings of this analysis are further supported by the by-time point analysis that excluded the 10-msec threshold and by the lack of outliers in the categorical analysis.

17.2. Laboratory Pancreatic Enzyme Analyses

[Figure 23](#) shows the Applicant's plot of mean serum lipase levels in study MG0010 by visit (day) and treatment group. The nominal 95% confidence intervals (CIs) in [Figure 23](#) suggest a significant difference between the zilucoplan 0.3 mg/kg and placebo groups. Serum amylase also showed a peak at day 57 but smaller, and not shown in this figure.

Figure 23. Study MG0010: Mean (95% CI) Change in Serum Lipase Level by Visit and Treatment Group.

Source: Applicant's Figure.

As shown in [Figure 23](#), the zilucoplan group had a 44 U/L increase in mean lipase level between baseline and day 57 (mean lipase went from 56 U/L to 104 U/L, not shown), as compared to 2 U/L in the placebo group. At day 84, mean lipase remained above baseline by 27 U/L, while the placebo group stayed 4 U/L above baseline. Although the day 57 mean included a single value of 1,987 U/L, removal of that data point had little impact on the appearance of the curve. Other subjects had serum lipase levels that also exceeded 3x ULN that were not called an AE. Most of these data were not at a level of detail to determine whether abdominal pain was present, or if imaging was done. However, if abdominal pain had been present, the American College of Gastroenterology criteria⁵ (Tenner et al. 2013) for acute pancreatitis could have been met.

Another trend in [Figure 23](#) is the large increase in variability of lipase levels in the zilucoplan group beginning at day 57 and persisting through day 84. This means that a sizeable number of subjects still had serum lipase levels exceeding their baseline values, or newly developed them at days 57 and/or 87, despite the decreasing mean.

In study MG0010, the ULN for lipase varied from 100 to 130 U/L, depending on the laboratory. [Table 94](#) is a shift table for subjects with normal (N) lipase at baseline. No subjects in the placebo group had lipase >3x ULN.

⁵ American College of Gastroenterology (ACG) criteria for acute pancreatitis: "The diagnosis of AP is most often established by the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging."

Table 94. Study MG0010: Shift Table for Subjects With Normal Baseline Serum Lipase by Treatment Group

Treatment Group (Study MG0010)	Counts of Lipase Shift From Day 1 to [Day 57 or 84] ^a	
	N-N ^b	N-H ^c
PBO	75	6
Zilucoplan 0.3 mg/kg	65	12 ^d

Source: Reviewer-generated from ADLB (lab) dataset

^a p=0.053 (1-sided Z-test of two proportions)^b N-N denotes Normal (N) lipase at Day 1 and Normal (N) lipase at Days 57 or 84^c N-H denotes Normal (N) lipase at Day 1 and High (H) lipase at Days 57 or 84^d Includes four subjects with lipase >3xULN ranging from 309 to 981 U/L

In study MG0010 and not shown in [Table 94](#), seven subjects started with a high lipase at baseline (five subjects in the zilucoplan group versus two in the placebo group), and five (four zilucoplan versus one in placebo) remained high at day 84.

Of the unscheduled visits where lipase was obtained, there were 33 visits in 33 subjects (13 placebo and 20 zilucoplan 0.3 mg/kg). These visits included 11 rescue therapy visits (9 placebo, 2 zilucoplan), 6 early discontinuations (3 placebo, 3 zilucoplan), 15 unscheduled visits (7 placebo, 8 zilucoplan), and a safety follow-up visit (zilucoplan). Among the 33 unscheduled lipase visits, there were five subjects (1 placebo and 4 zilucoplan) with 6 high lipase values (ranging from 110 to 429 U/L).

Lipase >3x ULN in Study MG0010

[Table 95](#) is the shift table for normal to high (>3xULN) for study MG0010, where ‘N’ means normal and ‘H3’ means >3xULN (greater than 3 times upper limit normal). No subjects with normal lipase at baseline in the placebo group had a lipase >3xULN at days 57 or 84.

Table 95. Study MG0010: Shift Table for Subjects With Normal Baseline Serum Lipase to Lipase >3xULN at Days 57 or 84, by Treatment Group

Treatment Group (Study MG0010)	Counts of Lipase Shift from Day 1 to [Day 57 or 84]	
	N-N ^b	N-H3 ^c
PBO	88	0
Zilucoplan 0.3 mg/kg	80	6

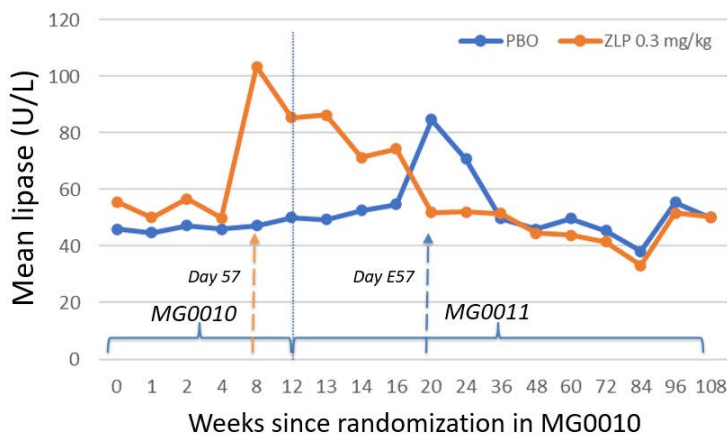
Source: reviewer generated from ADLB (lab) dataset

^b N-N denotes Normal (N) lipase at Day 1 and Normal (N) lipase at Days 57 or 84^c N-H3 denotes Normal (N) lipase at Day 1 and >3xULN lipase at Days 57 or 84

[Figure 24](#) is a reviewer-created figure that extends the mean lipase curves of [Figure 23](#) into MG0011.

Figure 24. Study MG0010-0011: Long-Term Mean Serum Lipase (U/L) by Treatment Group and Week Since Randomization in MG0010

Long-Term Mean Lipase (U/L) by Treatment Group in MG0010



Source: Reviewer-generated from ADLB datasets for studies MG0010 and MG0011

Figure 24 shows that peak mean lipase level in MG0010 occurred 57 days after starting zilucoplan 0.3 mg/kg, which is consistent with the Applicant's Figure 23 for MG0010. Figure 24 shows that in the placebo group, which started zilucoplan 0.3 mg/kg on day E1 of MG0011 (week 12 of MG0010), the peak once again occurs 57 days after beginning zilucoplan 0.3 mg/kg. The 95% CIs are not shown; however, high variability in lipase levels persisted in both groups through MG0011 when all subjects were on 0.3 mg/kg. This means that a sizable number of subjects still had values of serum lipase exceeding their baseline values or developed these increases during the extension studies despite the apparently decreasing mean value. To give another perspective on these long-term changes, I have created shift tables (below).

Table 96 is a shift table of subjects with normal lipase at days 57 or 84 of MG0010 to any visit in MG0011. There was a nominally statistically significantly larger proportion of subjects with normal (N) lipase in Study MG0010 at days 57 and 84 and high (H) lipase at any subsequent visit in MG0011 ($p=0.006$, 1-tailed Z-test of two proportions) in the zilucoplan group than the placebo group.

Table 96. Study MG0010-MG0011: Shift Table for Subjects With Normal Serum Lipase at Days 57 or 84 in MG0010 Compared to Serum Lipase at any Subsequent Visit in MG0011, by Original Treatment Group

Treatment Group (Study MG0010)	Lipase Shifts from MG0010 Day 57 or 84 thru any visit in MG0011 ^a	
	N-N ^b	N-H ^c
PBO	16	60
Zilucoplan 0.3 mg/kg	4	61

Source: reviewer generated from ADLB (lab) dataset

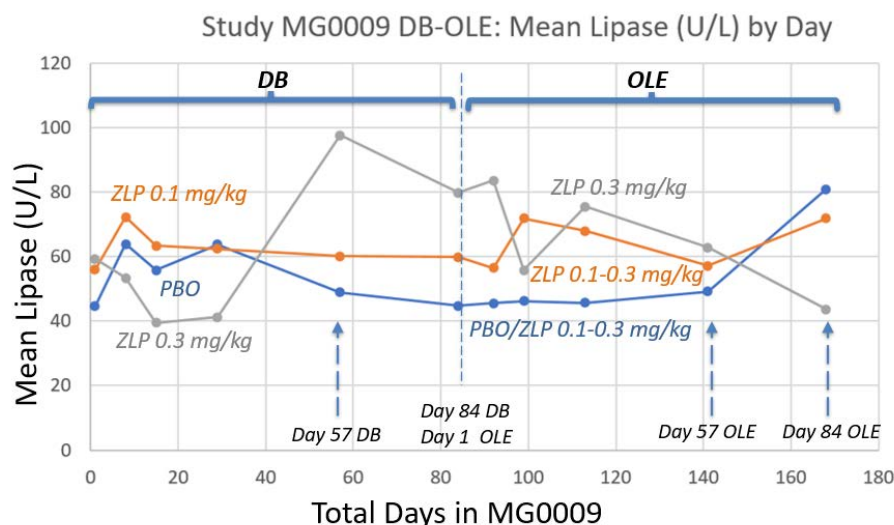
^a $p=0.006$ (1-sided Z-test for difference of two proportions)^b N-N denotes Normal (N) lipase at MG0010 Days 57 and 84, and Normal (N) lipase at any visit during MG0011^c N-H denotes Normal (N) lipase at MG0010 Days 57 and 84, and High (H) lipase at any visit during MG0011

Table 96 shows that significantly fewer subjects in the zilucoplan group ($n=4$) than in the placebo group ($n=16$) had normal lipase level at the end of MG0010 (beginning of MG0011) and

at any time during MG0011; and that most subjects after being started on zilucoplan in MG0011 had high lipase in MG0011, despite a normal level at the beginning of MG0011.

In study MG0009 double-blind portion, the results were similar. [Figure 25](#) shows mean lipase levels from randomization to the double-blind portion of MG0009 through its extension phase. Again, mean lipase in the zilucoplan 0.3 mg/kg group peaked at Day 57, as in study MG0010.

Figure 25. Study MG0009 DB and OLE: Mean Serum Lipase (U/L) by Randomization Group and Total Days in MG0009



Source: reviewer created from ADLB (lab) dataset for MG0009

In [Figure 25](#), the nominal 95% CIs are not shown, as they overlap considerably at all visits due to the small group sizes. During the double-blind period of MG0009, mean lipase increased by 40 U/L from baseline to day 84 in the zilucoplan 0.3 mg/kg group, which is close to the 44 U/L increase at the same dose in study MG0010. Also similar is the net increase from baseline to day 84, which is 20 U/L for study MG0009 compared to 27 U/L for study MG0010.

For placebo subjects in MG0009 who rolled into the MG0009 OLE, the peak mean lipase was at day 84 but had started to increase at day 57. This was likely related to not all patients in MG0009 OLE being on the 0.3 mg/kg dose because of a protocol amendment during the study, as follows. At the end of the double-blind period of MG0009, placebo subjects were randomized 1:1 to zilucoplan 0.1 mg/kg or 0.3 mg/kg, and then all subjects in all extensions (including MG0011) were changed to 0.3 mg/kg at some point pursuant to a protocol amendment. Therefore, the actual overall zilucoplan exposure in the [original] placebo arm of Study MG0009 exceeded 0.1 mg/kg but was less than 0.3 mg/kg during the extension, and this may explain the delayed peak.

[Table 97](#) shows mean serum lipase levels (with nominal 95% CI and maximum lipase value) for the double-blind period of MG0009 at days 1 and 84, by treatment group. It suggests an exposure-response trend for change in mean lipase from day 1 (i.e., baseline) to day 84 (final visit, or end-of-study), where mean lipase increased by 0, 4, and 21 U/L in the placebo, zilucoplan 0.1 mg/kg, and 0.3 mg/kg zilucoplan dose groups, respectively; however, the 95% CIs overlap considerably.

Table 97. Study MG0009 DB Portion: Mean (95% CI) Serum Lipase at Days 1 and 84

Mean Lipase (95% CI) [max] in U/L at Days 1 and 84			
Visit	PBO n=15	Zilucoplan 0.1 mg/kg n=15	Zilucoplan 0.3 mg/kg n=13
Day 1	45 (33, 56) [98]	56 (41, 71) [110]	59 (26, 93) [273] ^a
Day 84	45 (31, 59) [118]	60 (41, 79) [170]	80 (50, 110) [233] ^a

Source: reviewer generated from ADLB (lab) dataset

^a Subject (b) (6)

[Table 97](#) includes one subject ((b) (6), zilucoplan 0.3 mg/kg group) who had the highest day-1 lipase level (273 U/L). This subject's lipase normalized by day 15 (37 U/L) and remained low (36 U/L) at day 29, after which it increased to 120 U/L at day 57 and then to 233 U/L at day 84, which was again the highest lipase of all subjects in this table at the day 84 visit.

[Table 98](#) is the shift table for the double-blind period of study MG0009 for subjects with normal (N) lipase at baseline (i.e., day 1). [Table 98](#) shows the number of subjects with normal lipase (N-N) or high lipase (N-H) at days 57 or 84 by treatment group and suggests a general trend. Five (11%) subjects (two on placebo, three on zilucoplan 0.3 mg/kg, and none on zilucoplan 0.1 mg/kg) had >3x ULN lipase elevations after baseline, which occurred at days 8, 29, 57, and 84; one subject in the zilucoplan group had a >3xULN elevation at baseline, but not after that.

Table 98. Study MG0009 DB: Shift Table for Subjects With Normal Baseline Serum Lipase by Treatment Group

Treatment Group (Study MG0009 DB)	Counts of Lipase Shift from Day 1 to [Day 57 or 84]	
	N-N ^b	N-H ^c
PBO	10	2
Zilucoplan 0.1 mg/kg	8	1
Zilucoplan 0.3 mg/kg	6	5

Source: reviewer generated from ADLB (lab) dataset

^b N-N denotes Normal (N) lipase at Day 1 and Normal (N) lipase at Days 57 or 84^c N-H denotes Normal (N) lipase at Day 1 and High (H) lipase at Days 57 or 84

In the double-blind period of study MG0009 and not shown in the table is that some subjects had high (H) lipase level at baseline – 3 placebo, 5 zilucoplan 0.1 mg/kg, and 3 zilucoplan 0.3 mg/kg. Of the 3 PBO subjects, 2 remained high (H) at day 84; of the 6 zilucoplan 0.1 mg/kg subjects, 5 remained high (H) at day 84; and of the 3 zilucoplan 0.3 mg/kg subjects, all three subjects remained high (H) at day 84.

Amylase Level >3x ULN in the Laboratory Data. The above discussion addresses lipase only, as it is more sensitive and specific than amylase for pancreatitis. However, considering that amylase >3xULN is one of the American College of Gastroenterology criteria for acute pancreatitis, the cases of high-amylase AEs and amylase elevations in the laboratory data were examined as well.

There were two lab values with serum amylase >3xULN, both in study MG0011—one subject who had been on placebo in MG0010 had a high amylase level (785 U/L) at visit E8 (day 8 of MG0011), and the other who had been on placebo in MG0009 and had a high amylase level (321 U/L) at visit E108.

18. Clinical Virology

Not Applicable.

19. Clinical Microbiology

Not Applicable.

20. Mechanism of Action / Drug Resistance

Not Applicable.

21. Other Drug Development Considerations

Not Applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

There were data integrity issues in the narratives and pooled (ISS) and individual analysis dataset of adverse events and ADLB datasets. At least seven IRs were issued between January and July 2023 for these datasets. The problems involved all three studies and pooled datasets. They included missing data and records (including one death from pancreatic cancer—subject (b) (6), blank treatment-emergent flags, irreconcilable AE record counts, erroneously low values for liver and renal lab data and eosinophil counts in study MG0010, deviations that appeared in the pdf listing but not the deviations dataset. Most of the important issues with the narrative data was resolved. AE record counts changed with each amendment, and there was difficulty reconciling between or within study AE counts.

The Office of Scientific Investigations (OSI) identified several protocol deviations at three sites, although OSI assessed that study MG0010 appeared to have been conducted adequately and the data generated from these sites appeared acceptable for this indication. There was no evidence of under-reporting of adverse events. Several protocol deviations occurring at Site #119 involved 3 (21%) of 14 subjects taking anticholinergic inhibitors <10 hours before administration of the MG-ADL and QMG. According to onsite documents, these deviations were not identified until the date of database lock one to two years after the deviations had occurred. The statistical reviewer did a sensitivity analysis of the effect of these deviations on the primary endpoint and found that they did not change the statistical decision to reject the null hypothesis in favor of zilucoplan.

OSI issued an information request to the Applicant to submit data clarification forms (DCF) and audit trails for changes to the MG-ADL and QMG scores. OSI found that changes to MG-ADL and QMG scores occurred in 20 (11.5%) of 174 randomized subjects for 27 study visits. The majority of data changes were for QMG scores and were related to spirometry data (e.g., forced vital capacity). Overall, there were few data changes, and only one pertained to the primary endpoint efficacy data (MG-ADL scores at the timepoints of interest).

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the (Applicant's draft PI) ([Table 99](#)). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 99 Key Labeling Changes and Considerations

(b) (4)

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Instructions for Use
- Carton
- Container
- REMS documents

24. Postmarketing Requirements and Commitments

PMR 4487-1

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to zilucoplan during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

Draft Protocol Submission Date:	05/2024
Final Protocol Submission Date:	03/2025
Interim Report Dates:	03/2026
	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
	03/2034
Study Completion Date:	03/2035

Final Report Submission Date: 03/2036

PMR 4487-2

Perform a lactation trial (milk only) in lactating women who have received therapeutic doses of zilucoplan using a validated assay to assess concentrations of zilucoplan in breast milk and the effects on the breastfed infant as applicable.

Draft Protocol Submission Date: 04/2024
Final Protocol Submission Date: 02/2025
Study Completion Date: 07/2026
Final Report Submission Date: 12/2026

25. Financial Disclosure

Table 100. Covered Clinical Studies: MG0009 and MG0010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 547547		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None		
Significant payments of other sorts:		
Proprietary interest in the product tested held by investigator: reported No		
Significant equity interest held by investigator: reported No		
Sponsor of covered study: Ra Pharmaceuticals now UCB		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Click here to enter text.		
Is an attachment provided with the reason:	Yes ☐	No (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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27. Review Team

Table 101. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Michael Matthews / Heather Bullock
Nonclinical reviewer	Ed Fisher
Nonclinical team leader	Lois Freed
OCP reviewer(s)	Poonam Delvadia
OCP team leader(s)	Bilal AbuAsal
Pharmacometrics reviewer	Jie Liu
Pharmacometrics team leader	Atul Bhattaram
Deputy Director for Safety	Sally Jo Yasuda
Clinical reviewer	John Troiani
Deputy Director and cross-disciplinary team leader	Laura Jawidzik
Biometrics reviewer	Joanne Liu
Biometrics team leader	John Lawrence and Jim Hung
Associate Director Labeling	Tracy Peters
Division director (clinical)	Emily Freilich
Office director (or designated signatory authority)	Teresa Buracchio

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 102. Additional Reviewers of Application

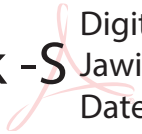
Office or Discipline	Name(s)
OPQ	Martha Heimann, Erica Keafer, Venkateswara (Venkat) Pavuluri, Katie Duncan, Gaetan Ladouceur, Khalid Khan, Cassandra Abellard, Helen Ngai, Paul Dexter
OPDP	Annette Egbonim and Aline Moukhtara
OSI	Cara Alfaro and Phillip Kronstein
OSE/DEPI	Silvia Perez-Vilar and Kira Leishear
OSE/DMEPA	Millie Shah and Colleen Little Judine Berlus (DMAMES)
OSE/DRM	Katie Holman, Anahita Tavakoli, and Jacqueline Sheppard, Lindsey Crist, Barbara Bergquist, Jo Wyeth, Sevan Kolejian
Immunogenicity	Ha-Na Lee and Daniela Verthelyi
DMPP consult	Lonice Carter and Marcia Williams
CDRH consult	Papatya Kaner and Courtney Evans

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

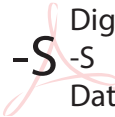
27.1. Reviewer Signatures

See next page.

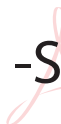
Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Signatory Authority	Teresa Buracchio Office of Neuroscience	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Teresa Buracchio -S Digitally signed by Teresa Buracchio -S Date: 2023.10.16 12:17:33 -04'00'				
Clinical Division Director	Emily Freilich Office of Neuroscience DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Emily R. Freilich -S Digitally signed by Emily R. Freilich -S Date: 2023.10.16 09:09:11 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Deputy Division Director and Cross-Discipline Team Lead	Laura Jawidzik Office of Neuroscience DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Digitally signed by Laura A. Jawidzik -S Date: 2023.08.25 09:12:11 -04'00'				
Clinical Primary Reviewer	John Troiani Office of Neuroscience DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 2, 3, 4, 6, 7, 8, 15, 17, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Deputy Division Director and Cross-Discipline Team Lead	Laura Jawidzik Office of Neuroscience DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: John Troiani -S Digitally signed by John Troiani -S Date: 2023.08.25 10:49:35 -04'00'				
Clinical Primary Reviewer	John Troiani Office of Neuroscience DN1	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 2, 3, 4, 6, 7, 8, 15, 17, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Other	Sally Jo Yasuda Office of Neuroscience DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: PMRs	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp:  Digitally signed by Sally U. Yasuda -S Date: 2023.08.25 10:26:33 -04'00'				
Product Quality Team Leader	Martha Heimann ONDP DNDPII	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Digitally signed by Martha R. Heimann Date: 2023.08.25 10:11:23 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Team Leader	Bilal AbuAsal Office of Clinical Pharmacology DNP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 6.1, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Bilal Abu Asal -S Digitally signed by Bilal Abu Asal -S Date: 2023.08.22 08:56:37 -04'00'				
Clinical Pharmacology Primary Reviewer	Poonam Delvadia Office of Clinical Pharmacology DNP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 6.1, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Poonam R. Delvadia -S Digitally signed by Poonam R. Delvadia -S Date: 2023.08.09 12:38:19 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology/Pharmacometrics Team Leader	Atul Bhattaram Office of Clinical Pharmacology DNP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Venkatesh A. Bhattaram -S Digitally signed by Venkatesh A. Bhattaram -S Date: 2023.08.25 10:49:05 -04'00'				
Clinical Pharmacology/Pharmacometrics Primary Reviewer	Jie Liu Office of Clinical Pharmacology DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Jie Liu -S Digitally signed by Jie Liu -S Date: 2023.08.25 10:04:37 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Team Leader	John Lawrence Office of Biostatistics DB1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Digitally signed by John P. Lawrence -S Date: 2023.08.18 09:56:00 -04'00'				
Biometrics Primary Reviewer	Joanne Liu Office of Biostatistics DB1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Jinnan Liu -S


 Digitally signed by Jinnan Liu -S
 Date: 2023.08.18 12:25:18 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacology/Toxicology Deputy Director	Lois Freed Office of Neuroscience DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13.1, and 13.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Lois M. Freed -S Digitally signed by Lois M. Freed -S Date: 2023.08.25 11:50:19 -04'00'				
Pharmacology/Toxicology Primary Reviewer	Ed Fisher Office of Neuroscience DPTN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13.1, and 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: J Edward Fisher -S Digitally signed by J Edward Fisher -S Date: 2023.08.25 09:52:45 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Management CPMS	Heather Bullock Office of Neuroscience DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Heather M. Bullock -S Digitally signed by Heather M. Bullock -S Date: 2023.08.17 16:13:54 -04'00'				
Regulatory Project Management Regulatory Project Manager	Michael Matthews Office of Neuroscience DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Michael Matthews -S Digitally signed by Michael Matthews -S Date: 2023.08.17 15:55:19 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Associate Director for Labeling	Tracy Peters Office of Neuroscience DN1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 22	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  August 25, 2023				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
10/17/2023 10:29:02 AM