STATISTICAL ANALYSIS PLAN

AMENDMENT 2.0

Study: RA101495-02.202 (UCB study IMNM01)

Product: Zilucoplan

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF ZILUCOPLAN IN SUBJECTS WITH IMMUNE-MEDIATED NECROTIZING MYOPATHY

Ra Pharmaceuticals, Inc. (now part of UCB)

Legal Registered Address:

Ra Pharmaceuticals, Inc.

87 Cambridge Park Drive

Cambridge, MA, 02140, USA

Regulatory Agency Identifier Number(s):

Registry	ID
EudraCT Number	2019-001497-29

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study RA101495-02.202 (UCB study IMNM01) is based on the protocol amendment dated 16 February 2021.

SAP Version	Approval Date	Change	Rationale
1.0	11 February 2020	Not Applicable	First Creation
Amendment 1	18 February 2021	Sections / Paragraphs numbers are renumbered / reorganized	Update to meet UCB Standards / Template
		Data description and precision rules	Update to meet UCB Standards / Template
		Text is added to describe analyses for all efficacy endpoints and list the estimand attributes	To align with the protocol amendment 2, dated 16 February 2021
		Abbreviation List is updated	Ensure abbreviations are used in the appropriate way
		Addition of populations: ITT No COVID-19 Safety Set No Covid-19 Additional summaries based on COVID-19 subgroups, pre or during the COVID-19 pandemic	Update analysis to include COVID-19 strategy
		The following populations are defined: Enrolled Set Intention to Treat Extension Pharmacodynamic Per-Protocol Set Pharmacokinetic Per-Protocol Set	To capture all the analysis populations
		RA101495 Safety Population is deleted	Information is redundant
		Disposition on all participants enrolled and screen failures is defined	To display the disposition of screen failures as per UCB guidance
		Definition of treatment exposure is added	Information was missing
		Categories of prior and concomitant medications are defined	Further clarification
		Age and BMI cutoffs are introduced in the summary statistics	To describe the parameters summarized in more details

SAP Version	Approval Date	Change	Rationale
		Demographics and baseline characteristics will not be compared between IMPs	To map the UCB policy
		Summaries on Related of IMNM and non-IMNM related medications are added	To describe the parameters summarized in more details
		Analysis based the Van Elteren test is upgrade to primary analysis	To align with protocol amendment 2, dated 16 February 2021
		Wilcoxon Mann Whitney Odds estimation Hodges–Lehmann estimator are added.	To align with the protocol amendment 2, dated 16 February 2021
		Main analysis of the primary and secondary efficacy endpoints is changed from the Last Observation Carried Forward approach (LOCF) to observed case analysis. LOCF was downgraded to supplementary analysis.	To follow the treatment policy of the study estimands based on the protocol amendment 2, dated 16 February 2021
		Separate Wilcoxon signed rank tests for each IPM will not be implemented	Information is not relevant
		The following text has been deleted: "No control for multiplicity will be applied for the secondary endpoint analyses in this Phase 2 study"	Team's decision
		Secondary endpoints are re-ordered to define the hierarchy and setting the multiplicity controls	To control multiplicity
		Analysis using trimmed mean approach was added as supportive analysis	To present sensitivity analysis for robustness of the results if necessary
		Further analysis based on CK is added: a. responder analysis of percentage change from baseline based on 80%, 50% and normalization b. analysis based on logCK is added	To provide additional information on the CK response

SAP Version	Approval Date	Change	Rationale
		MMRM modeling for the CK percentage change from baseline to Week 8 was deleted	Team's decision
		Linear Mixed Effects Models instead of Mixed Models for Repeated Measures to be employed for main analysis of Secondary Endpoints; model covariates are re-defined	To reduce the degrees of freedom in the model for better convergence due to limited number of participants analyzed
		Any inferential statistics related to the Primary and Secondary Endpoints will be performed only at Week 8 and complementary at Week 4.	To reduce multiple testing
		Individual items within each performance outcomes, clinician-reported outcome and patient-reported outcomes will not be tested between Investigational Medicinal Products (IMPs).	Team's decision
		Definition of baseline derivation during the Main Portion was updated	To provide more clarity
		Definition of study relative day and study periods is added	To provide more clarity
		Imputation of any missing dates and time was redefined	To map the UCB guidance
		Calculation rules for the AE duration are added	To align across UCB programs
		Adverse Events of interest were introduced	To align with UCB safety guidance
		Update the AE summaries during the Extension with Exposure Adjusted Incidence Rate	To provide additional exposure information for the AEs
		TEAEs occurring in the first 8 Weeks of the Extension Period in the subjects who received placebo in the Main portion and subsequently received 0.3 mg/kg in the Extension Portion will not be summarized separately."	Information will be captured in listings

SAP Version	Approval Date	Change	Rationale
		Markedly Abnormal (MA) values for the lab parameters, ECG and Vital signs are defined	To align with UCB safety policy
		Inferential analysis of lab parameters during the main and/or extension portion is removed	Team's decision
		The analysis of immunogenicity related to anti-drug antibodies (ADA) is clarified	To provide more clarity and better understanding of the data
Amendment 2	09 June 2021	Table 6.3 CTCAE v5.0 grades for laboratory assessments to be analyzed, is updated as follows:	
		1.Total Bilirubin (TBL) (standard) changed from Umol/L to µmol/L	To provide clarity on units employed
		2. Creatinine units (standard) changed from Umol/L to µmol/L	To provide clarity on units employed
		3. CRP units (conventional) changed from "mg/L" to "mg/dL"; CRP units (standard) changed from	To correctly display the conventional and standard CRP units used in study
		4.CRP Markedly Abnormal criteria changed from ">10mg/L; >100 g/L" to ">10mg/dL >100 mg/L"	To align the CRP Markedly Abnormal criteria with published literature
		5.Potassium units (conventional) were updated from "mmol/L" to "mEq/L"	To correctly display the conventional Potassium units used in study datasets
		6.Potassium Marked Abnormality criterion (low) was changed from "<2.5mmol/L" to "<3.0mmol/L"	To align with CTCAE v5, November 17th, 2017
		7.Sodium conventional units were updated from mmol/L to mEq/L	To correctly display the conventional Sodium units used in study datasets
		9.Marked Abnormality Criterion for WBC high abnormal values was added: High: >100 x 10^9/L	To align with CTCAE v5, November 17, 2017
		10.Marked Abnormality Criterion for AST changed from >5.0xULN to >5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal	To align with CTCAE v5, November 17, 2017

SAP Version	Approval Date	Change	Rationale
		11.Marked Abnormality Criterion for ALT changed from >5.0xULN to >5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal	To align with CTCAE v5, November 17, 2017
		12.Marked Abnormality Criterion for ALP changed from >5.0xULN to >5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal	To align with CTCAE v5, November 17, 2017
		13.Marked Abnormality Criterion for γ-GT changed from >5.0xULN to >5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal	To align with CTCAE v5, November 17, 2017
		14.Marked Abnormality Criterion for low corrected calcium abnormal values was changed to: Low: Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L	To align with CTCAE v5, November 17, 2017
		15. Table row indicating "Triglycerides" assessment is deleted	Triglycerides lab values are not part of the study assessments
		Adverse of Interest regarding "Hepatic events and drug-induced liver injuries, Drug related hepatic disorders"	To capture the specific Adverse of Interest accurately
		Abbreviation of PCSA is added	To provide more clarity
		"Markedly Abnormal Criteria" terminology for ECG and vital sings is replaced with Abnormality Criteria. Corresponding text within the body of the SAP is amended accordingly.	Team's decision

SAP Version	Approval Date	Change	Rationale
		Reference is added: Karbhari, DS, Karbhari, NS, Patel, S (2017). Significance of measurement of corrected calcium in patients with normoalbuminemia. International Journal of Medical Science and Public Health 1069-1071.	To support the derivation of Corrected Calcium

LIST OF ABBREVIATIONS

aPTT	activated Partial Thromboplastin Time
ALQ	Above Limit of Quantification
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
AE	Adverse Event
AEIR	Adverse Event Incidence Rate
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of Covariance
anti-HMGCR	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
anti-SRP	Signal Recognition Particle
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
bpm	Beats per minute
BSL	Baseline
BUN	Blood urea nitrogen
Ca	Calcium
C5	Complement component 5
CI	Confidence Interval
CK	Creatine Kinase
CPStat	Clinical Program Biostatistician
CRP	C-Reactive Protein
CS	Completer Set
CSR	Clinical Study Report
CTStat	Clinical Trial Biostatistician
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid

LIST OF ABBREVIATIONS

DRM	Data Review Meeting
eCRF	electronic Care Report Form
EDV	Early Discontinuation Visit
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
ES	Enrolled Set
EAER	Exposure Adjusted Event Rate
EAIR	Exposure Adjusted Incidence Rate
eGFR	estimate Glomerular Filtrate Rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	US Food and Drug Administration
γ-GT	gamma-Glutamyl Transferase
geoCV	geometric Coefficient of Variation
HAQ	Health Assessment Questionnaire
ICH	International Council for Harmonisation
ICE	Intercurrent Event
IMNM	Immune-Mediated Necrotizing Myopathy
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviations
ITT	Intention to Treat
ITT_{EXT}	Intention to Treat - Extension
$ITT_{NoCOVID-19}$	Intention to Treat No Covid-19
IVIG	Intravenous Immunoglobulin G
kg	Kilograms
LDH	Lactate dehydrogenase
LLoQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LPFV	Last Participant First Visit
LPLV	Last Participant Last Visit
LSM	Least Squares Mean

LIST OF ABBREVIATIONS

LSMD	Least Squares Mean Difference
MA	Markedly Abnormal
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDAAT	Myositis Disease Activity Assessment Tool
MedDRA	Medical Dictionary for Regulatory Activities
MMT	Manual Muscle Testing
ms	millisecond
OR	Odds Ratio
PDILI	Potential Drug Induced Liver Injury
PBO	Placebo
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamic
PD-PPS	Pharmacodynamic Per Protocol Set
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PSOC	Primary System Organ Class
PT	Preferred Term
PTT	Partial prothrombin time
PEY	Participant-years exposure
QoL	Quality of Life
QTc(F)	Fridericia corrected QT interval
RS	Randomized Set
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
scIg	Subcutaneous Immunoglobulin

LIST OF ABBREVIATIONS

SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
sRBC	Sheep red blood cell
SS	Safety Set
$SS_{NOCOVID-19}$	Safety Set No Covid-19
TBL	Total bilirubin (blood)
TEAE	Treatment-Emergent Adverse Event
TFL	Tables Figures and Listings
VAS	Visual Analogue Scale
WBC	White Blood Cell
WMWodds	Wilcoxon-Mann-Whitney odds
3TUG	Triple Timed Up and Go Test

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all the necessary information of the full statistical methodology to be performed for the statistical analysis of the IMNM01 study (legacy Ra Pharma study RA101495-02.202) which is sponsored by UCB S.A.

The content of this SAP and the statistical methodology described, is compatible with the International Council for Harmonisation guidance documents (ICH E9, ICH E9(R1) addendum).

Data will be analyzed by eClinical Solutions Contract Research Organization (CRO) based on the methodology described at the study protocol amendment 2 (dated 16 February 2021) and the current SAP amendment 2. Any changes and/or deviations from the study protocol are documented in Section 6.3.

This SAP includes efficacy, safety, immunogenicity, pharmacokinetics [PK], pharmacodynamics [PD] data, that covers the entire study duration.

Summary tables figures and listings (TFLs) to be included in the Clinical Study Report(s) (CSR) are defined in the current document. TFLs specifications are stated in a separate document. If deemed appropriate, Statistical Analysis System (SAS) outputs and details for critical statistical analysis will be made available and placed in the corresponding CSR appendix.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP may be amended accordingly.

1.1 Objectives and Estimands/Endpoints

The estimands corresponding to the analysis of the primary and secondary objectives are described below:

Table 1–1: Objectives and Estimands/Endpoints

Objectives	Estimands / Endpoints
Primary Efficacy Objective	
To evaluate the efficacy of Zilucoplan over placebo in creatinine kinase (CK) levels in participants with IMNM	Primary Estimand: • Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo • Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population • Endpoint: Percent change from Baseline to Week 8 in CK levels; • Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after prohibited medication; • Population level summary: difference in ranks of the percentage change from Baseline between treatment conditions followed by the Wilcoxon-Mann-Whitney odds (WMWodds) and Hodges–Lehmann estimator.

Table 1–1: Objectives and Estimands/Endpoints

Objectives	Estimands / Endpoints
Primary Safety Objective	
To evaluate the safety Zilucoplan over placebo in creatinine kinase (CK) levels in participants with IMNM	Primary Safety Endpoint: • Incidence of Treatment-emergent Adverse Events
Secondary Efficacy Objective	
To further evaluate the efficacy of Zilucoplan over placebo in participants with IMNM	Secondary Estimands: • Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo • Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol, reflecting the targeted IMNM population • Endpoints: – At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at Week 8; – Change from Baseline to Week 8 in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only); – Change from Baseline to Week 8 in Proximal Manual Muscle Testing (MMT); – Change from Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS); – Change from Baseline to Week 8 in Patient Global Activity Visual Analogue Scale (VAS); – Change from Baseline to Week 8 in Health Assessment Questionnaire (HAQ); – Change from Baseline to Week 8 in MDAAT Extramuscular Disease Activity VAS Score; – Change from Baseline to Week 8 in FACIT-Fatigue Scale. • Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication • Population level summary:

Table 1–1: Objectives and Estimands/Endpoints

Objectives	Estimands / Endpoints
	– Odds Ratio (OR) of ACR/EULAR ≥ 20 response proportion between treatment conditions; – Difference in continuous endpoint means, between treatment conditions.
Other Safety Objective	
To further evaluate the safety of Zilucoplan over placebo in participants with IMNM	Other Safety Endpoints • Change in clinical laboratory tests • Change in ECG parameters • Change in vital signs parameters • Presence of Anti-Drug Antibodies
Exploratory Objectives	
To assess the long-term efficacy of Zilucoplan	• At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at each visit following Week 8; • Change from Baseline of Timed Up and Go (3TUG) Test (in ambulatory patients only) at each visit following Week 8; • Change from Baseline of Proximal Manual Muscle Testing (MMT) at each visit following Week 8; • Change from Baseline of Physician Global Activity Visual Analogue Scale (VAS) at each visit following Week 8; • Change from Baseline of Patient Global Activity Visual Analogue Scale (VAS) at each visit following Week 8; • Change from Baseline of Health Assessment Questionnaire (HAQ) at each visit following Week 8; • Change from Baseline of MDAAT Extramuscular Disease Activity VAS Score at each visit following Week 8; • Change from Baseline of FACIT-Fatigue Scale at each visit following Week 8;
To assess the PK Zilucoplan	Plasma concentrations of Zilucoplan and its major metabolites
To assess the PD of Zilucoplan	• Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation

Table 1–1: Objectives and Estimands/Endpoints

Objectives	Estimands / Endpoints
	• Complement component 5 (C5) levels
To assess the effect of Zilucoplan on biomarkers	Mechanistic biomarkers [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), myocyte markers, and inflammatory markers].
To assess the effect of Zilucoplan on pharmacogenomics	Pharmacogenomic analyses (optional): Genomic studies [e.g., deoxyribonucleic acid (DNA) sequencing, including exploration of whether specific genomic features correlate with response or resistance to study drug], may be performed.

1.2 Study design

IMNM01 is a multicenter, randomized, double-blind, placebo-controlled parallel study to evaluate the safety, tolerability and efficacy of Zilucoplan in IMNM cases who are positive for anti-HMGCR (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) or anti-SRP (signal recognition particle) autoantibodies.

The planned enrollment is approximately 24 participants.

Participants are randomized at Day 1 to 1:1 ratio in order to receive:

- daily SC doses of 0.3 mg/kg Zilucoplan (12 participants), or
- matching placebo administered SC (12 participants).

Randomization is stratified based on the antibody status (anti-HMGCR+ versus antiSRP+).

Following in-clinic education and training all participants will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 8 weeks. Single use pre-filled syringes in injection devices are provided for use during the study.

All standard of care therapy medications for IMNM should be kept at the same doses throughout the study, including corticosteroids, immunosuppressive drugs, and IVIG.

The study is comprised of the Main Portion and the Extension Portion. The Main Portion of the study includes a Screening Period of up to 4 Weeks and an 8 Week Treatment Period.

During the Treatment Period, participants will return to the clinic at Week 1, Week 2, Week 4 and Week 8 for safety, tolerability and efficacy evaluations.

Efficacy assessments include Creatine Kinase (CK) levels, as well as performance outcomes, clinician-reported outcomes and patient-reported outcomes (PRO).

Safety assessments include physical examination, vital signs, electrocardiogram (ECG), clinical laboratory tests, adverse event (AE) monitoring and immunogenicity.

Additional assessments include biomarker testing, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics.

At the end the study Treatment Period, participants have the option to receive Zilucoplan in the Extension Portion of the study provided they meet the Extension Portion selection criteria. Visits during the first 8 Weeks of the Extension Portion are identical to the Main Portion of the study for all participants to ensure appropriate monitoring of participants transitioning from placebo to active treatment.

The study remains double-blinded until after the data from the Week 8 Main Portion have been reviewed, locked and unblinded. If a participant permanently discontinues study treatment prior to Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For participants who permanently discontinue treatment with study drug, a Safety Follow-up Visit is performed 40 days after the last dose to collect information on any ongoing AEs or new SAEs since last visit.

Schedule of Assessments at Table 1–2 and Table 1–3 illustrate the time and events schedule for the Main Portion and the Extension Portion of the study.

Table 1–2: Schedule of Assessments During the Main Portion of the Study

			Week 1	*Week 2*	*Week 4*	*Week 8*	
Study Procedure	Screening Days –28 to –1	Day 1 (Baseline)	Day 8 (±2 days)	Day 15 (±2 days)	Day 29 (±2 days)	End of Main[a] Study Day 57 (±7 days)	Safety Follow-up Visit (last dose + 40d)
Informed consent[b]	X						
Review eligibility[b]	X						
Randomization		X					
Medical history[c] and demographics	X						
Height[d] and weight	X				X	X	
Prior and concomitant medications[e]	X	X	X	X	X	X	X
Safety							
Physical examination	X	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X
12-lead ECG	X					X	
Neisseria meningitidis vaccination[g]	X						
Prophyfactic antibiotics[g] *(if applicable)*		X	X	X			
Hematology / Chemistry / CK[h]	X	X	X	X	X	X	
Coagulation[h, i]	X	X	X	X	X	X	
Urinalysis[h]	X	X	X	X	X	X	
Pregnancy test[j]	X	X	X	X	X	X	X
Adverse Events[k]	X	X	X	X	X	X	X[k]
Anti-Drug Antibody[h]	X		X		X	X	
Efficacy							

Table 1–2: Schedule of Assessments During the Main Portion of the Study

			Week 1	*Week 2*	*Week 4*	*Week 8*	
Study Procedure	Screening Days –28 to –1	Day 1 (Baseline)	Day 8 (±2 days)	Day 15 (±2 days)	Day 29 (±2 days)	End of Main[a] Study Day 57 (±7 days)	Safety Follow-up Visit (last dose + 40d)
3TUG[l, m]	X	X			X	X	
Proximal MMT[l]	X	X			X	X	
Physician Global Activity VAS[l]	X	X			X	X	
Patient Global Activity VAS[l]	X	X			X	X	
HAQ[l]	X	X			X	X	
MDAAT[l]	X	X			X	X	
FACIT-Fatigue[l]	X	X			X	X	
Pharmacokinetic / Pharmacodynamic							
Zilucoplan plasma PK[n]		X	X	X	X	X	
Pharmacodynamic analysis[n]		X	X	X	X	X	
Exploratory							
Autoantibodies testing[o]	X	X			X	X	
Biomarker testing[p]		X	X	X	X	X	
Pharmacogenomic analysis *(optional)*[q]	X	X					
Study Drug							
Zilucoplan or placebo administration[r]		X	X	X	X	X	

[a] If a subject permanently discontinues study drug prior to completion of the Day 57 visit during the Main Portion, the subject should return to clinic for an End of Main Visit. If a participant consents to the Extension Portion, please see Table 1–3 for Day 57/E1 assessments. If a subject permanently discontinues study drug treatment prior to the Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For subjects who permanently discontinue treatment with study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose to collect information on any ongoing AEs or new SAEs since the last study visit.

[b] Procedures performed as standard of care during the Screening Period may be used to determine eligibility. Informed consent must be obtained prior to performing any study-specific procedures that are not standard of care. Eligibility must be established prior to randomization on Day 1.

[c] Screening includes a detailed history of IMNM diagnosis information and local serology for anti-HMGCR or anti-SRP autoantibodies from a reputable laboratory.

[d] Height will be measured only at Screening

[e] All prescriptions and over-the-counter medications taken during the 30 days prior to Baseline (i.e., Day 1) through the last study visit will be documented. NOTE: A complete history of all medication taken for the treatment of IMNM will be collected.

[f] The vital signs assessment will include measurement of HR, body temperature, and blood pressure in the sitting position.

[g] To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local standard of care, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) until at least 2 weeks after initial dose of vaccine(s). Booster vaccinations should be administered in accordance with local standard of care. NOTE: In participants who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) should be given upon initiation of study drug until 6 months after the last rituximab dose.

[h] All laboratory samples should be obtained prior to administration of study drug at applicable visits.

[i] Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

[j] For all female subjects of childbearing potential, a negative serum pregnancy test must be documented at Screening. All other pregnancy tests will be performed via urine.

[k] All AEs and SAEs should be monitored until resolution or stabilization. SAEs that occur within 40 days after the last dose of study drug should be reported using the procedures outlined in the protocol. Participants will attend a clinic visit 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit. Only SAEs are collected during the screening period.

[l] The clinical assessments should be performed at approximately the same time of day (preferably in the morning) and should be administered in the same order by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) at each visit throughout the study.

[m] 3TUG will only be completed in subjects who are ambulatory.

[n] Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing).

[o] Confirmatory serology testing for anti-HMGCR or anti-SRP autoantibodies will be done at a central laboratory.

[p] Blood samples for biomarker testing will be obtained prior to administration of study drug (within 1 hour of dosing).

[q] The pharmacogenomic sample may be collected at any study visit.

[r] Dosing on study visit days should be held until clinical assessment and blood collection has been completed.

Table 1–3: Schedule of Assessments During the Extension Portion of the Study

	Month 2			*Month 3*	*Month 4*	*Month 5*	*Month 6*	*Visits after Day E117*			
Study Procedure	Day E1[a] (Day 57)	Day E8 (±2 days)	Day E15 (±2 days)	Day E29 (±2 days)	Day E57 (±2 days)	Day E87 (±7 days)	Day E117 (±7 days)	Each Month (±7 days)	Every 3 Months (±7 days)	Final Extension Visit[b]	Safety Follow-up Visit (last dose + 40d)
Informed consent	X										
Review eligibility and randomization	X										
Weight	X			X	X		X		X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Safety											
Physical examination	X	X	X	X	X		X		X	X	X
Vital signs[c]	X	X	X	X	X		X		X	X	X
12-lead ECG	X				X				X		
Neisseria meningitidis vaccination[d]	X	Standard of Care	Standard of Care	Standard of Care	Standard of Care	Standard of Care	Standard of Care	Standard of Care	Standard of Care		
Hematoloy / Chemistry / CK[e]	X	X	X	X	X		X		X	X	
Coagulation[e,f]	X	X	X	X	X		X		X	X	
Urinalysis[e]	X	X	X	X	X		X		X	X	
Pregnancy test[g]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X[h]
Anti-Drug Antibody[e]	X	X		X	X		X		X	X	
Efficacy											

Table 1–3: Schedule of Assessments During the Extension Portion of the Study

	Month 2			*Month 3*	*Month 4*	*Month 5*	*Month 6*	*Visits after Day E117*			
Study Procedure	Day E1[a] (Day 57)	Day E8 (±2 days)	Day E15 (±2 days)	Day E29 (±2 days)	Day E57 (±2 days)	Day E87 (±7 days)	Day E117 (±7 days)	Each Month (±7 days)	Every 3 Months (±7 days)	Final Extension Visit[b]	Safety Follow-up Visit (last dose + 40d)
3TUG[i, j]	X			X	X		X		X	X	
Proximal MMT[i]	X			X	X		X		X	X	
Physician Global Activity VAS[i]	X			X	X		X		X	X	
Patient Global Activity VAS[i]	X			X	X		X		X	X	
HAQ[i]	X			X	X		X		X	X	
MDAAT[i]	X			X	X		X		X	X	
FACIT-Fatigue[i]	X			X	X		X		X	X	
Pharmacokinetic / Pharmacodynamic											
Zilucoplan plasma PK[k]	X	X	X	X	X		X		X	X	
Pharmacodynamic analysis[k]	X	X	X	X	X		X		X	X	
Exploratory											
Autoantibodies testing	X			X	X		X		X	X	
Biomarker testing[l]	X	X	X	X	X		X		X	X	
Study Drug											
Zilucoplan or placebo administration[m]	X	X	X	X	X	X	X	X	X	X	

[a] For participants that decide and are eligible to continue in the Extension Portion of the study, the Day 57 visit from the Main Portion will serve as the Day E1 visit and will also include review of eligibility to continue and signing of an informed consent for the Extension Portion.

administered in the same order by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) at each visit throughout the study.

[b] If a participant discontinues study drug treatment at any time during the Extension Portion, the participant should return to clinic for a Final Extension Visit.

[c] The vital signs assessment will include measurement of HR, body temperature, and blood pressure in the sitting position.

[d] During the Extension Portion of the study, all participants should have Neisseria meningitidis booster vaccinations as indicated by standard of care. Participants should bring their patient safety card to every study visit. If a participant does not bring the card, then a new one will be given to him/her.

[e] All laboratory samples should be obtained after clinical assessments and prior to administration of study drug at applicable visits.

[f] Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

[g] Urine pregnancy tests will be conducted in female subjects of childbearing potential.

[h] All AEs and SAEs should be monitored until resolution or stabilization. SAEs that occur within 40 days after the last dose of study drug should be reported using the procedures outlined in the protocol. Participants will attend a clinic visit 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit.

[i] The clinical assessments should be performed at approximately the same time of day (preferably in the morning) and should be administered in the same order by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) at each visit throughout the study.

[j] 3TUG will only be completed in subjects that are ambulatory.

[k] Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing).

[l] Blood samples for the exploratory tests will be obtained prior to administration of study drug (within 1 hour of dosing).

[m] Dosing on study visit days should be held until clinical assessment and blood collection has been completed.

2 STATISTICAL HYPOTHESES

The hypotheses to be included in the testing strategy are listed at the next sections; type 1 error will be set such that a family wise type 1 error of 5% is maintained.

The primary hypothesis H_{01} will be tested at 2-sided α=5%. Should H_{01} is rejected then the whole α will be passed to the next hypothesis until all hypotheses are rejected. Of note, the level of a rejected hypothesis should only pass on the next testing only if the treatment effect is in favour of Zilucoplan.

2.1 Primary endpoint

The Null Hypothesis for the primary endpoint is that there is no treatment difference in Week 8 between Zilucoplan and placebo treatment conditions in the percentage change from baseline of CK levels.

The Null Hypothesis (H_{01}) asserts that it is equally likely to one treatment group to be less than or greater than the other splitting ties evenly:

Let Y1 and Y2 be observations drawn independently from the two IMP (Investigational Medicinal Products) distributions.

Then:

- H_{01}: π= 0.5 for both strata, where π = Prob(Y1 < Y2) + 1/2 Prob(Y1 = Y2) and
- H_{A1}: $\pi_i \neq 0.5$ for at least one stratum (Alternative Hypothesis)

Converting π to an odds measure: WMWodds = π / (1 – π) the H_{01} and H_{A1} can be re-written as:

- H_{01}: WMWodds = 1
- H_{A1}: WMWodds ≠ 1

2.2 Secondary endpoints

$H_{02.1}$: Zilucoplan is not different to placebo regimen with respect to the proportion of patients achieving at least minimal response based on the ACR/EULAR Response Criteria Scale

$H_{02.2}$: Zilucoplan is not different to placebo regimen with respect to change from baseline in Triple Timed Up and Go (3TUG) Test to Week 8 among ambulatory patients

$H_{02.3}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in Proximal Manual Muscle Testing (MMT)

$H_{02.4}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS)

$H0_{2.5}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in Patient Global Activity VAS

$H_{02.6}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in Health Assessment Questionnaire (HAQ)

$H_{02.7}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in MDAAT VAS Score in the Extramuscular Disease Activity item

$H_{02.8}$: Zilucoplan is not different to placebo regimen with respect to change from baseline to Week 8 in FACIT-Fatigue Scale

3 SAMPLE SIZE DETERMINATION

A sample size of 12 study participants per group yields approximately 95% power to detect a difference in the percent reduction from baseline in creatine kinase between the active and placebo groups using a Wilcoxon rank sum test at the two-sided 0.05 type 1 error rate.

The power calculations assume that the percent reduction in creatine kinase in the active dose group is approximately normally distributed with a mean of 80% and a standard deviation of 8%; that 4 of the placebo patients will have a percent reduction similar to the active dose group; and the remaining 8 placebo patients will have a percent reduction that is normally distributed with a mean of 10% and a standard deviation of 8% (Mammen and Tiniakou 2015).

4 POPULATIONS FOR ANALYSIS

- **Enrolled Set (ES):** will include in all screened participants including screen failures.
- **Intention-to-Treat Population (ITT):** will include all randomized participants.
- **$ITT_{NoCOVID-19}$:** will include all ITT participants excluding those with confirmed COVID-19 as observed during any visit of the Main Portion of the study and reported in the AE eCRF form.

  Of note, $ITT_{NOCOVID-19}$ will be considered in any analysis specified in the current document during the Main Portion only, provided it differs by at least 15% from the ITT in terms of number of participants.
- **Per Protocol Set (PPS):** will include all participants in the ITT Population who have completed the 8 Week Treatment Period and have no important protocol deviations. Important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

  If a participant received multiple doses of different study drug (i.e., placebo and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Main Portion of the study.
- **Intention to Treat - Extension (ITT_{EXT}):** will include all participants who entered the Extension Portion of the study.
- **Safety Set (SS):** will include all participants who received at least 1 dose of study drug during the Main Portion of the study irrespective if they continued to the Extension Portion. Participants will be analyzed based on the actual treatment received.

If a study participant received multiple doses of different study drug (i.e., placebo and 0.3 mg/kg), the participant will be assigned to the dose group which he/she received at the highest frequency within the Main Portion of the study.

Of note, participants who were on placebo during the Main Portion of the study and continued to the Extension Portion will be included in both groups depending on the study period assessed. Safety results on 0.3 mg/kg across the Main and Extension Portions will be combined.

- **Safety Set No Covid-19 ($SS_{NOCOVID-19}$)**: will include all participants in the SS except those with confirmed COVID-19 (as reported in AE eCRF form) during any time of the study (Main or Extension Portion).

  Of note, $SS_{NOCOVID-19}$ will be considered in any analysis specified in the current document, provided it differs by at least 15% from the ITT in terms of number of participants.

- **Pharmacokinetic Per-Protocol Set (PK-PPS):** will include those study participants in the SS who received 1 dose, had at least 1 valid PK measurement post first dose of study treatment, and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock.

- **Pharmacodynamic Per-Protocol Set (PD-PPS):** will include those study participants in the SS who received 1 dose, had at least 1 valid PD measurement post first dose of study treatment, and no important protocol deviations affecting the PD variable, as confirmed during a pre-analysis review of the data prior to database lock.

5 STATISTICAL ANALYSES

5.1 General Considerations

- Descriptive statistics for continuous endpoints will include number of participants with available measurements (n), mean, standard deviation (SD), median, 25% and 75% percentiles, minimum and maximum. Confidence Intervals (CIs) will be provided where appropriate. In general, all study endpoints will be summarized descriptively by IMP and overall (if applicable).

- Frequencies and percentages will be presented by IMP for categorical and ordinal variables. Unless otherwise noted, the denominator for percentages will be based on the number of participants included in the respective analysis set.

Participants with missing data can generally be accounted for using the following approaches:

- For summaries of demographics and baseline characteristics: summarize percentages based on all participants in the analysis set and include a "Missing" category (corresponding to participants with missing data for the variable being summarized) as the last row in the list of categories being summarized. Percentages are associated with the missing row so that percentages sum to 100.

- For summaries of efficacy and safety variables, unless otherwise specified: summarize percentages based only on those participants with observed data for the variable being summarized. As the denominator may be different from the number of participants in the

analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)."

All percentages will be displayed with one decimal place. No percentage will be displayed for zero counts and no decimals will be presented when the percentage is 100%. If there are no missing data for a variable, then the missing row can be removed for that variable in the shell. If there are no observations in any specific eCRF-specified category, then retain that row and present 0's across the table. E.g., if there are no 'American Indian/Alaskan native' participants in the study but this was one of the Racial Group categories in the eCRF, then retain the row and populate it with 0 values.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer;
- Mean, SD, and percentiles will use one additional decimal place compared to the original data reported;
- CV [%] will be presented with one decimal place;
- Minimum and maximum will have the same number of decimal places as the original value reported.

Derived variables in general will be displayed to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied, then either the maximum raw number of reported decimal places or 3 will be used, whichever is the lowest.

If no participants have data at a given time point, for example, then only n=0 will be presented. However, if n<3, present the n, minimum and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank.

If for a particular output there are no valid cases to summarize for any variable, then report "No data observed".

Demographics and baseline characteristics will be analyzed in ITT. Separate tables based on the enrollment date relative to 11 Mar 2020 will be created.

Efficacy analyses will be performed primarily in the ITT population. Prior and Concomitant medications summaries will be performed in the SS. Medical History will be analyzed in the ITT. Safety, PK and PD analyses will be performed primarily in the SS, PK-PPS and PD-PPS.

Comparative efficacy analysis (inferential statistics) will focus on the Main Portion of the study only where both active and placebo treatments are given in blinded manner.

Baseline is defined in Section 5.1.1.2.4.

Change from Baseline is defined as: post baseline value - baseline value.

Percentage Change from Baseline is defined as: 100 x (Change from Baseline/Baseline), if baseline is greater than zero.

IEs are defined as these events that may preclude an observation from the study or affect the interpretation of the results; in the current setting the following is considered as IE:

- Intake of medication which is prohibited by the protocol (complement inhibitor, rituximab, statins, or any investigational medicinal product while on study)

Since the primary analysis of the primary and secondary endpoints will be based on treatment policy estimand (that is, observed case analysis) the only data manipulation to be considered is the censoring of efficacy values following to the administration of any prohibited medication.

5.1.1 General study level definitions

5.1.1.1 Analysis visit windows

All data will be analyzed based on the visits identified per the schedule of activities in protocol. Mapping to analysis visit windows will not be applied, except for end of treatment (EDV) visits (specified in Section 5.1.1.2.3).

5.1.1.2 Analysis Time Points

5.1.1.2.1 Relative day

- For days on or after the day of first dose of study drug and prior to or on the day of last study drug dose (e.g., the day of 1st dose will be Day 1,) the relative day will be calculated as:
- For days after the last dose of study drug, the relative day will be calculated as:
- For days prior to the 1st dose of study drug, the relative day will be calculated as:
- Relative day will not be calculated for partial dates and it must be left blank in these instances.

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a participant data listing. In such cases, relative day should be presented as '- -' in the participant data listings.

5.1.1.2.2 Study periods

- **Screening Period** is defined as any time prior to the date/time of first dose of study drug and after the date/time of the ICF signature. Screening period starts at maximum 28 days prior to the randomization day.
- **Treatment** Period is defined as the period on or after the date/time of the first dose of study drug and ends at the date/time of Week 8 visit or at the date/time the participant has performed the End of Study Visit prior to Week 8. If a participant does not have a Week 8 visit or End of Study Visit, then either the date of the last scheduled or unscheduled visit during the Main Portion or the date of the last known dose of study drug during the Main Portion, whichever is later, will define the end date of Blinded Period.
- **Follow-up Period** starts one day after the Week 8 visit and ends after the final assessments on the safety Follow-up visit (40 days later). For participants who permanently discontinue the study during the treatment period, the follow-up period starts the next day and ends 40 days later after the final safety assessments. Participants with assessments after the blinded period

are considered to have started the Follow-up Period provided, they have not entered the Extension Portion of the study.

- **Extension Period** starts one day after the end of Treatment Period and lasts until the day of the final extension visit.
- **Extension Follow-up Period** starts one day after the end of the final extension visit and ends at the day when final assessments are performed on the safety Follow-up visit (40 days later).

5.1.1.2.3 Mapping of assessments performed at Early Discontinuation Visit

If a participant prematurely discontinues treatment at any time during the Main Portion, then he/she should return to the clinic for a stand-alone End of Main Visit. Corresponding assessments will be mapped to the next visit scheduled where each assessment is done as per protocol.

5.1.1.2.4 Definition of Baseline values

Unless otherwise specified, the Baseline value for the Treatment Period is defined as the most recent (date/time considered) non-missing value obtained prior to the administration of the first study dose. If there are multiple assessments on that day then the time will be considered for the selection of the appropriate measurement. For parameters with no Baseline value as per schedule of assessments the screening value will be set as Baseline value. If a Baseline measurement is not available but an unscheduled measurement occurs after the planned Baseline measurement time point but before dosing, then the unscheduled measurement will be used.

For participants who received placebo in the Treatment Period, the value obtained prior to the first administration of Zilucoplan will occur on the Day E1 (Day 57) visit during the Extension Portion of the study and this will be the Baseline value for them for any summary tables during the Extension Portion of the study. If Day 57 dose is missing the last non-missing dose on placebo during the Main Portion will define the baseline date for the placebo patients who change to active in Extension Portion.

5.1.1.3 Protocol Deviations

Important protocol deviations (IPDs) are deviations from the protocol which potentially could have a meaningful impact on the study conduct or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual participant. IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. IPDs will be identified and documented prior to unblinding and will be utilized to decide which data will exclude study participants from the PPS and PK-PPS.

Analysis related to protocol deviations is described in Section 6.1.2.

5.1.1.4 Treatment assignment and treatment groups

SS and $SS_{NOCOVID-19}$ analyses will be based on the actual treatment received.

- If after unblinding it is determined that participants at any time received incorrect treatment as compared to the one they were randomized to, then these participants will be reallocated to the appropriate IMP. For example, if participants randomized to placebo received Zilucoplan, then for the safety and PK/PD analyses, these participants will be reallocated to Zilucoplan. Participants randomized to Zilucoplan will only be reallocated to the placebo IMP if they never received Zilucoplan. Placebo
- 0.3 mg/kg Zilucoplan
- All participants (if appropriate)

For specific safety analysis, data from the Main and the Extension Portion will be combined and summarized. Specifically, safety data of participants who received Zilucoplan 0.3 mg/kg during the Main Portion of the study will be combined with the Extension Portion safety data.

Efficacy data during the Extension Portion will be shown based on the combination of the randomized and treatment switch:

- Placebo - 0.3 mg/kg Zilucoplan
- 0.3 mg/kg Zilucoplan - 0.3 mg/kg Zilucoplan.

Following to the analysis of Week 8 Main Portion of the study, re-alignment based on duration of medication exposure might be considered if deemed necessary.

5.1.1.5 Center pooling strategy

All centers will be pooled together for the efficacy analysis of this study. **Coding dictionaries**

Adverse events (AEs) and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) using the existing version at the date of the database lock. The MedDRA version will be stated at each relevant table.

Medical procedures will not be coded.

Medications will be coded according to the Anatomical Therapeutic Chemical Classification system (ATC) / World Health Organization Drug Dictionary and (WHODD), using the existing version at the date of database lock. The version will be stated at each corresponding table.

5.1.1.7 Multicenter studies

This is a study targeting 24 participants and conducted at 18 sites. No efficacy results will be displayed by study site.

5.1.1.8 Handling of drop outs or missing data

5.1.1.8.1 Missing efficacy data

The rules for handling missing data of individual items in the calculation of the PROs and performance outcomes are described in Section 6.1.5.

Main Analysis

- No multiple imputation methodology will be considered with respect to the main analysis of the primary and secondary efficacy objectives.
- If a participant receives prohibited medication, then efficacy data will be censored at the date/time that he/she received the medication.

Sensitivity Analysis

- Trimmed means methodology with imputation at extreme unfavorable value for the primary objective of CK levels (if applicable based on SAP criterion, see Section 5.3.3).

5.1.1.8.2 Missing data due to Covid-19

Missing data is expected to be one of the implications of the COVID-19 pandemic. The following approaches/strategies will be applied to assess the impact of COVID-19 in this study.

- Added an eCRF page "COVID-19 Impact", including impacted visits, and reasons.
- Additional fields were added in protocol deviation specification documents to record protocol deviations relationship to COVID-19.
- Included additional summary analyses based on the timing of COVID-19 impact (pre or during the COVID-19 pandemic period).
- An overall summary of number of visits impacted by COVID-19 by IMP.
- Summary on numbers of actual visits performed for each nominal visit (along with the summary on the primary reason the assessments were impacted (COVID-19 Precaution Measures / Participant was Diagnosed with COVID-19).

5.1.1.8.3 Missing dates and times

Partially or completely missing dates may be imputed for the following reasons:

- Classification of AEs as TEAEs;
- Classification of medications as past, prior, or concomitant medications;

Imputed dates will not be shown in listings (dates will be displayed as reported in the database).

The following rules will be applied for partially or completely missing start dates:

- If year, month and day are all missing then assign the date of first dose of study intervention. If an imputed start date is after the specified end date, then assign January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).
- If month and day are missing, and year is:
  - the same as the year of the first dose of IMP then assign the month-day of first dose of IMP. If the imputed start date is after the specified end date, then assign January 01, or the month-day of screening date if this is later (if the latter imputation results in an end date that is earlier than the start date, then assign January 01);

- not the same as the year of the first dose of IMP then assign January 01.

- If only day is missing and month-year is:
  - the same as the month-year of the first dose of IMP then assign the day of first dose of IMP. If the imputed start date is after the specified end date, then assign first day of the month, or the day of screening date if this is later (if the latter imputation results in an end date that is earlier than the start date, then assign first day of the month);
  - not the same as the month-year of the first dose of IMP then assign the first day of the month.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, then use discharge date or data cut-off date.

Date of discontinuation, the date of last contact will be used as the discharge date. For participants still ongoing at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

In the event of ambiguity or incomplete data that makes it impossible to determine whether a medication was concomitant, the medication will be considered as concomitant. Similarly, in the event of ambiguity or incomplete data which makes it impossible to determine whether a medication is to be assigned to the Main Portion or to the Extension Portion of the study or both, then the medication will be assigned to both study portions.

The following rules are applied to impute partial onset and resolution dates for AEs. AEs with partial onset date are classified as either non-treatment- or treatment-emergent based on the imputed onset date. The imputed onset date is also used to classify TEAEs by study portion or into time intervals. Each TEAE should be classified into exactly one study portion for the classification of TEAEs into study periods.

Imputation of Partial Onset Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of onset, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose is the same as the month and year of onset, then use the date/time of first dose
- If only the year is specified, and the year of first dose is not the same as the year of onset, then use January 1 of the year of onset
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date/time of first dose
- If the AE onset date is completely unknown, then use the date of first dose

Imputation of Partial Resolution Dates (if needed)

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of that year
- If the stop date is completely unknown, then use discharge date or data cut-off date.

Note: Discharge date refers to the date of the end of study visit for completed participants or the date of discontinuation for participants that were withdrawn. For any AEs with known start date after the date of discontinuation, the date of last contact will be used as the discharge date. For participants still ongoing in the study at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

Consequently, AE duration will be calculated as stop date – start date + 1.

In the event of ambiguity or incomplete data that makes it impossible to determine whether an AE was treatment emergent, the AE will be considered treatment emergent. Similarly, in the event of ambiguity or incomplete data which makes it impossible to determine whether an AE is to be assigned to the Main Portion of the study or to the Extension study portion, then the AE will be assigned to the Main Portion.

5.2 Participant Disposition

To assess the impact of COVID-19, a table based on the ITT (overall and by IMP) for each country (and overall) will indicate the number of participants at each visit performed, number of participants with missed visits, number of participants with telephone calls or video calls performed. Corresponding listing will be created in ES.

A separate table by IMP for the Main and Extension Portion will provide details on subjects discontinued due to AEs. More precisely, the number and percentage of participants who discontinued the study due to AE (AEs leading to discontinuation of only the following type: serious fatal, non-fatal, non-serious fatal) will be presented.

5.3 Primary Endpoint(s) Analysis

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population
- Endpoint: percentage change from baseline to Week 8 in CK levels
- Intercurrent event handling: regardless of any treatment discontinuation for any reason; censoring after prohibited medication
- Population level summary: difference in ranks of the percentage change from baseline between treatments followed by the Wilcoxon-Mann-Whitney odds (WMWodds) and Hodges–Lehmann estimator.

The statistical hypothesis being tested at Week 8 is that there is no difference in the percentage change from baseline in CK levels between Zilucoplan and placebo as described at Section 2.1.

5.3.1 Definition of endpoint(s)

The primary endpoint is the percentage change from baseline of CK levels at Week 8, defined as:

$\%CHG = 100 \times (Value_{WEEK8} - Value_{BSL}) / Value_{BSL}$

5.3.2 Main analytical approach

The statistical hypothesis is stated at Section 2.1. The analysis will be conducted in the ITT using a 2-sided Van Elteren test (Van Elteren, 1960) which stands for an extension of the Wilcoxon rank sum test for comparing two treatments in a stratified experiment using within-stratum ranks assigning greater weight to rank sums from smaller strata.

The magnitude of association between groups will be expressed as in WMWodds followed by the 95% CI and by the Hodges–Lehmann estimator which quantifies the location shift.

WMWodds will be estimated based on the weighted average WMWodds for the strata. The methodology is described below:

- For each stratum the WMWOdds will be calculated via ROC analysis for the CK levels.
- The derived AUC and SE values will be used for the calculation of the stratified WMWOdds:

  $WMWodds_i = AUC_i/(1-AUC_i)$, $i=1,2$

  The $WMWodds_i$ and the Standard Error (SE) will be transformed to the logarithmic scale to ensure positive values of the corresponding 95%CIs:

  $LnWMWodds_i = Ln(AUC/(1-AUC_i))$, $i=1,2$

  $LnSE_i = SE_i/(AUC_i*(1-AUC_i))$, $i=1,2$
- Inverse variance weights will be assigned at each strata: $W_i = 1/(LnSE_i * LnSE_i)$, $i=1,2$:
- The weighted average WMWodds ($\overline{WMWodds}$) and the corresponding 95%CI can be then calculated as shown below:

$$(\overline{WMWodds}) = \exp\left(\frac{\sum_{i=1}^{i=2} Wi * LnWMWoddsi}{\sum_{i=1}^{i=2} Wi}\right)$$

$$95\%CI = \exp\left(\left(\frac{\sum_{i=1}^{i=2} Wi * LnWMWoddsi}{\sum_{i=1}^{i=2} Wi}\right) \pm Z_{0.025} * 1/\sqrt{\sum_{i=1}^{i=2} Wi}\right)$$

Additionally, for the unweighted WMWodds and Hodges–Lehmann estimator followed by the corresponding 95%CI, will also be calculated.

5.3.3 Sensitivity analyses

Analysis based on Van Elteren test and on trimmed means methodology (Permutt 2017) in ITT if at Week 8 at least 15% of participants do not have evaluable CK results. All missing data will be

imputed at an extreme unfavorable value. A permutation-based test will be carried out, with the trimming fraction applied adaptively at 1000 treatment permutations. The fraction trimmed will be chosen adaptively as that greatest of the proportion of missings in the group.

First, data should be ordered and trimmed by equal fractions, always trimming all drop outs. Then, the summary measure will be computed based on the trimmed data. Previous steps to be repeated on permuted data to construct a reference distribution for testing and interval estimation.

Estimand:

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population
- Endpoint: percentage change from baseline to Week 8 in CK levels
- Intercurrent event: regardless of any treatment discontinuation for any reason; censoring after prohibited medication
- Population level summary: difference in ranks of the percentage change from baseline between treatments followed by trimmed means

5.3.4 Supplementary analyses

- Analysis methodology mentioned in Section 5.3.2 will be repeated in ITT using the LOCF approach; that is any Week 8 missing data for any reason will be imputed by the closest non-missing value of the parameter.
- Analysis methodology mentioned in Section 5.3.2 will be repeated in PPS.
- Analysis methodology mentioned in Section 5.3.2 will be repeated in $ITT_{NOCOVID-19}$.

Further analysis within the ITT population, based on the percentage change of CK levels from baseline to Week 4 and Week 8 will be considered as indicated below:

Definition of Estimand(s):

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population
- Endpoints:
  - (A): percentage change from baseline to Week 4 in CK levels
  - (B): change from baseline to Week 4 and to Week 8 in Log_{10}CK levels
  - (C): Week 4 and Week 8 response defined as at least 80% reduction in CK levels

- (D): Week 4 and Week 8 response defined as at least 50% reduction in CK levels
- (E) Week 4 and Week 8 CK levels within normal range

- Intercurrent events: regardless of treatment discontinuation due to lack of efficacy, or any AE, death; censoring after prohibited medication
- Population level summary:
  - (A): difference in ranks of the percentage change from baseline between treatment conditions followed by the Wilcoxon-Mann-Whitney odds (WMWodds) and Hodges–Lehmann estimator;
  - (B): difference in mean change from baseline to Week 4 and Week 8 of Log10CK between treatment conditions;
  - (C), (D), (E): OR of response proportion categories between treatment conditions;

For the population level summary (A): analysis will be performed as described in Section 5.3.2.

For the population level summary (B): analysis will be based on linear mixed effects model. As response variable will be the change from baseline to Week 4 and to Week 8 respectively. Treatment and strata will be fitted as fixed factors whereas baseline levels of the parameter as covariate; participants will be fitted at random. The Kenward-Roger approximation will be used to estimate the denominator's degrees of freedom. The antilogs of the least squares means (LSMs) of each IMP and the least squares mean differences (LSMDs) between the Zilucoplan and placebo will be reported for the Week 8 and Week 4 change from baseline, along with the corresponding 2-sided 95% CIs and p-values.

For the population level summary (C, D, E): Analysis will be performed via logistic regression model with treatment and stratification factors included for each response parameter; the OR of Zilucoplan over placebo will be given followed by the 95% CI.

Corresponding summary statistics will be presented in each IMP.

5.4 Secondary Endpoint(s) Analysis

5.4.1 Key/Confirmatory secondary endpoint(s)

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol, reflecting the targeted IMNM population
- Endpoints:
  - At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at Week 8;
  - Change from Baseline to Week 8 in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only);

- Change from Baseline to Week 8 in Proximal Manual Muscle Testing (MMT);
- Change from Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS);
- Change from Baseline to Week 8 in Patient Global Activity Visual Analogue Scale (VAS);
- Change from Baseline to Week 8 in Health Assessment Questionnaire (HAQ);
- Change from Baseline to Week 8 in MDAAT Extramuscular Disease Activity VAS Score;
- Change from Baseline to Week 8 in FACIT-Fatigue Scale;

- Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication
- Population level summary:
  - Odds Ratio (OR) and ACR/EULAR ≥ 20 response proportion between treatment conditions;
  - Difference in continuous endpoint means between treatment conditions

5.4.2 Definition of endpoint(s)

- ACR/EULAR response is defined based on the total improvement score, see Section 6.1.5.7 for the response criteria. The endpoint of minimal response is defined as achievement of ACR/EULAR ≥ 20 at Week 8.
- Absolute change from baseline to Week 8 of:
  - 3TUG,
  - Proximal MMT,
  - Physician Global Activity VAS,
  - Patient Global Activity VAS,
  - HAQ,
  - Extramuscular Disease Activity VAS Score of MDAAT Score and
  - FACIT-Fatigue Scale.

  Change from baseline to Week 8 (CHG_{Week8}) of each secondary continuous endpoint is defined as: $CHG_{Week8} = (Value_{Week8}-Value_{BSL})$.

5.4.3 Main analytical approach

Analysis to determine the OR and the 95%CI of ACR/EULAR ≥ 20 (minimal treatment response) between IMPs will be performed via binary logistic regression with IMP and strata as fixed factors. Bar charts by treatment will be created to illustrate the treatment effect.

In order to assess secondary efficacy for any continuous parameter, a separate linear mixed effect model will be employed for each secondary continuous efficacy parameter. At each linear mixed effect model, the response variable will be the change from baseline to Week 8. Treatment and strata will be fitted as fixed factors whereas baseline levels of the parameter as covariate; participants will be fitted at random. The Kenward-Roger approximation will be used to estimate the denominator's degrees of freedom. The least squares means (LSMs) of each IMP and the least squares mean differences (LSMDs) between the Zilucoplan and placebo will be reported for the Week 8 change from baseline along with the corresponding 2-sided 95% CIs and p-values.

Statistical estimators based on Least Square Means (LSMs) and Standard Errors (SE) or 95%CIs will be plotted for each treatment.

5.4.4 Sensitivity analysis

No sensitivity analysis to be performed.

5.4.5 Supplementary analyses

Analysis mentioned at Section 5.4.3 will be repeated in ITT with missing values imputed based on the LOCF approach from the previous non missing visit of Week 8. Based on this approach, the elements of ACR/EULAR will also be imputed with the last non missing parameter in order the score to be calculated at Week 8.

Analysis mentioned at Section 5.4.3 will be repeated in the $ITT_{NOCOVID-19}$. In case of non-convergence, only the summary statistics will be reported.

Analysis mentioned at Section 5.4.3 will be repeated in the PPS.

Estimand:

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population
- Endpoints:
  - ACR/EULAR of at least minimal response at Week 4;
  - ACR/EULAR ordinal treatment esponse at Week 4 and Week 8;
  - ACR/EULAR Total Improvement Score at Week 4 and Week 8;
  - Change from Baseline to Week 4 in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only);
  - Change from Baseline to Week 4 in Proximal Manual Muscle Testing (MMT);
  - Change from Baseline to Week 4 in Physician Global Activity Visual Analogue Scale (VAS);

- Change from Baseline to Week 4 in Patient Global Activity Visual Analogue Scale (VAS);
- Change from Baseline to Week 4 in Health Assessment Questionnaire (HAQ);
- Change from Baseline to Week 4 in MDAAT Extra muscular Disease Activity VAS Score;
- Change from Baseline to Week 8 in FACIT-Fatigue Scale;

- Intercurrent event: regardless of treatment discontinuation for any reason; censoring after administration of prohibited medication;
  - Population level summary: Odds Ratio (OR) of ACR/EULAR ≥ 20 response proportion between treatment conditions (analysis will be performed as mention Section 5.4.3).
  - Population level summary: ACR/EULAR ordinal treatment response proportion in treatment conditions;
  - Difference in continuous endpoint means between treatment conditions (analysis will be performed as mention Section 5.4.3).

For the determination of ACR/EULAR response categories, see Section 6.1.5.7. Ordinal ACR/EULAR treatment response (no improvement, minimal improvement, moderate improvement, major improvement) at Week4 and Week 8 will be only be summarized by IMP.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

5.5.1 Long Term Efficacy

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg)
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol, reflecting the targeted IMNM population
- Endpoints:
  - At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at each study visit following Week 8;
  - Change from Baseline in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only) at each study visit following Week 8;
  - Change from Baseline in Proximal Manual Muscle Testing (MMT) at each study visit following Week 8;
  - Change from Baseline in Physician Global Activity Visual Analogue Scale (VAS) at each study visit following Week 8;
  - Change from Baseline in Patient Global Activity Visual Analogue Scale (VAS) at each study visit following Week 8 at each study visit following Week 8;

  - Change from Baseline in Health Assessment Questionnaire (HAQ) at each study visit following Week 8;
  - Change from Baseline in MDAAT Extramuscular Disease Activity VAS Score at each study visit following Week 8;
  - Change from Baseline in FACIT-Fatigue Scale at each study visit following Week 8;
- Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication
- Population level summary:
  - ACR/EULAR ≥ 20 response proportion;
  - Mean change from Baseline to each extension portion visit

Further summaries by IMP to be provided for each ACR/EULAR response category (no response, minimal response, moderate response and major response) and for the ACR/EULAR TIS.

Analysis will be performed in descriptive manner without any statistical comparisons to be considered.

5.5.2 Mechanistic biomarkers

Blood samples for mechanistic biomarker testing [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers] will be obtained prior to administration of study drug (within 1 hour of dosing) as indicated at Table 1–2 and Table 1–3.

The analysis of biomarkers pertaining to the pathophysiology of IMNM [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), and inflammatory markers] may provide further insight into the clinical efficacy and safety of Zilucoplan in IMNM participants. Complement protein levels and complement activity will be tested to evaluate response to Zilucoplan and to understand participant characteristics related to variations in response to drug. Markers of inflammation may be tested to assess correlation with complement function and clinical response to Zilucoplan. A list of analytes will be created through review of the literature, ongoing clinical studies, and ongoing exploratory work and may be finalized after completion of the study. The completion of these investigations may be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome.

The results of the biomarker analysis will be reported separately from the main clinical study report analyses and therefore analysis will not be stated in this document.

5.5.3 Pharmacogenomic analyses (optional)

Participation in the pharmacogenomic assessment is optional, and participants must provide additional consent for the pharmacogenomic analysis. For cases who choose to participate in pharmacogenomic studies, a blood sample is obtained. All genomic analyses will be performed

at an accredited laboratory. Genomic studies (e.g., deoxyribonucleic acid (DNA) sequencing) including exploration of whether specific genomic features correlate with response or resistance to study drug, may be performed. The completion of these investigations may be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome.

The results of the genomic investigations will be reported separately from the main clinical study report analyses and therefore analysis will not be stated in this document.

5.6 Safety Analyses

5.6.1 Extent of Exposure

Any analysis related to the exposure will be based the SS.

The number and percentage of participants with cumulative IMP duration (e.g. any duration, ≥1 week, ≥2 weeks, ≥3 weeks,…., etc.) will be presented by IMP.

IMP duration = Date of Last Dose – Date of First Dose +1

The duration of exposure to each treatment will be summarized by IMP:

Duration of exposure in years (or Participant Exposure Years (PEY)) = [(min(Date of Last Dose + 40 days, Last Visit) - Date of First Dose+1)] /365.25

Thus, exposure will be adjusted for the 5 half-lives of active treatment which is 40 days.

Duration of exposure (100 participant years) = PEY / 100.

Summaries on the treatment exposure and time at risk in subject years will be given.

Participants which are exposed to both treatments will be presented in either study treatments using the corresponding start and stop treatment date.

The number of doses missed (from the eCRF Study drug administration page after Day 1) will be summarized overall and by IMP.

5.6.2 Adverse Events

Adverse events will be captured from the time of informed consent signature (only the SAEs) or from the time of first administration (Treatment Emergent Adverse Events) and will be reported if occurred during scheduled on unscheduled visits. As Treatment Emergent AE (TEAE) is defined as an AE starting on or after the time of first administration of study drug or an AE that increases in severity after treatment start, if the event was present at the time of the treatment initiation. Reporting of TEAEs refer to the period until the administration of the last study dose plus 40 days (or last visit depending which occurs first).

AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for severity. For any AE where it is not possible to provide a CTCAE grading, the event will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described below:

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3, 4, 5 - Severe

These will be tabulated together with the AEs that were not classified according to CTCAE criteria i.e., all Grade 1 AEs as per CTCAE criteria will be included in the 'mild' category together with those AEs classified as mild as per the 'standard' intensity classification.

If a particular AE severity is missing, then this will be listed as missing and treated as missing in summaries. If a participant has experienced more than one TEAE within the same PT, then the AE with the greatest severity will be presented. If a participant reported more than on AE within the same (System Organ Class) SOC then the participant will be counted only once with the greatest severity at the SOC where applicable.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless evidence exists that does not allow the AE to be treatment-emergent. Handling of missing dates for classification of AEs as TEAEs is described in Section 5.1.1.8.

TEAE summaries will be performed in SS and repeated in $SS_{NOCOVID-19}$ if at least 15% of the participants have at least one AE as 'Confirmed COVID-19'.

Summaries may also be repeated in SS among participants with at least one TEAT based on the COVID-19 period defined as:

- Before the pandemic: a TEAE will be assigned to this period if the start date of the event is on or after the date of the first administration of study drug on Day 1 but before the cut-off date of 11th MAR 2020.
- During/after the pandemic: a TEAE will be assigned to the during/after the pandemic Period if the start date of the event is on or after the date of the first administration of study drug on Day 1 but after the cut-off date of 11th MAR 2020.

A TEAE will be counted as related to study drug if the response to the question "Relationship to Study Medication" is "Related". Severe TEAEs are those with CTCAE Grade 3 or above, or those without a CTCAE grading classified as 'severe' by the Investigator. If a participant reports the same event with different relationship assessments, then participant will be counted under both related and not related categories.

Adverse events will be presented as "number of participants (percentage of participants) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual participants, while "number of participants" will count each participant only once.

TEAE Summaries will be reported separately within the Main Portion and within the Main and Extension Portion of the study and presented by primary system organ class (PSOC) and preferred term (PT) within each IMP. PSOCs will be sorted alphabetically. PTs will be sorted by decreasing frequency of Zilucoplan within each PSOC; ties will be sorted alphabetically within Zilucoplan. TEAEs will be mapped to a study portion based on the onset date.

The following summaries will be produced:

- TEAE overview table in SS and $SS_{NOCOVID-19}$, displaying participants with at least one TEAE, with at least one TEAE before/after 11th March 2020, with at least one serious TEAE, with at least one TEAE resulting to permanent withdrawal from study medication, with at least one drug-related TEAE and with at least one TEAE leading to death
- TEAEs by PSOC and PT, in SS
- TEAEs by PSOC and PT by COVID-19 period, in SS
- Serious TEAEs by PSOC and PT in SS
- Serious TEAEs by PSOC and PT for each COVID-19 period, in SS
- TEAEs by PSOC, PT and maximum CTCAE V5.0 Grade, in SS
- TEAEs by PSOC, PT and maximum relationship, in SS
- Serious TEAEs by PSOC, PT and maximum relationship, in SS
- Fatal TEAEs by PSOC, PT and maximum relationship, in SS
- Non-Serious TEAEs by PSOC and PT of at least 5% within any IMP (Main Portion) or active treatment (Extension Portion), in SS
- TEAEs by PSOC and PT leading to drug discontinuation, in SS
- TEAEs by PSOC and PT leading to death, in SS

Of note, the following are not considered to be AEs despite requiring hospitalization:

- Pre-existing conditions that, in the opinion of the investigator, did not worsen or progress during study participation
- Routinely scheduled procedures or treatments
- Elective procedures that were scheduled prior to study participation (i.e., signing of the ICF)

Safety tables for the combined Main and Extension Portion of the study, will display the Treatment Emergent Adverse Event Incidence Rate (AEIR) per 100 patient-years of Zilucoplan treatment (thus no placebo arm to be summarized due to limited exposure time as compared to active). Tables will include the PEY per 100 patient years (as defined in Section 5.6.1), number and percentage of participants with a particular TEAE, the exposure adjusted incidence rate EAIR) followed by 95%CI and the exposure adjusted event rate (EAER):

- EAIR for TEAEs by PSOC and PT, in SS
- EAIR for serious TEAEs by PSOC and PT, in SS

The EAIR is defined as the number of study participants with a specific new TEAE divided by the duration of exposure of all participants (scaled to100 participant years). The time at risk for a study participant is censored at the date of this event. If a study participant has no events, the total time at risk (i.e. exposure) is used.

Exact Poisson 95% CIs for EAIR are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990; Fay and Feuer, 1997):

$$Lower\ Confidence\ Limit = x^2_{2n,\alpha/2}/2$$

$$Upper\ Confidence\ Limit = x^2_{2n(n+1),1-\alpha/2}/2$$

where n stands for the number of participants with a specific TEAE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability $\chi 2$.

The EAER is defined as the total number of TEAEs including repeat occurrences in individual study participants divided by the total time at risk scaled to 100 patient-years. No confidence interval will be computed for the EAER.

Individual data listing of all AEs (TEAEs and non TEAEs) will be created and displayed by IMP based on the ES. Also, by participant listings for all the TEAEs leading to permanent withdrawal of study drug, for all the TEAEs related to study drug and for all the TEAEs leading to death will be presented by IMP. In each listing, a COVID-19 flag will be present indicating the time frame of the event relevant to the COVID-19 period. A separate data listing for participants with confirmed COVID-19 will be produced.

5.6.3 Adverse Events of Interest

The following bullets define the TEAEs of interest for Zilucoplan:

- **Infections**
  - Serious infections: Serious TEAEs in MedDRA SOC "Infections and infestations"
  - Infections: TEAEs in MedDRA SOC "Infections and infestations"
  - Neisseria infections: TEAEs in MedDRA HLT "Neisseria infections"
  - Serious Neisseria infections: Serious TEAEs in MedDRA HLT "Neisseria infections"
- **Adverse events potentially related to hypersensitivity (including anaphylaxis)**

Potential anaphylactic reactions are defined via a MedDRA algorithmic approach (see Section 6.2), which combines a number of different TEAEs/anaphylactic reaction symptoms. Some cases are dependent on the presence of multiple symptoms/TEAEs (i.e. TEAEs with the same AE onset day or one day later) in order to be classified as an anaphylactic reaction; at least one of the symptoms/TEAEs needs to be serious for the reaction to be classified as a serious anaphylactic reaction.

- Anaphylactic reactions are defined as follows:

  Serious Anaphylactic reactions: MedDRA algorithmic approach to anaphylaxis where at least one of the TEAEs needs to be serious

  Anaphylactic reactions: MedDRA algorithmic approach to anaphylaxis among TEAES
- Hypersensitivity reactions are defined as follows:

  Serious hypersensitivity reactions: Serious TEAEs in MedDRA Standardized MedDRA Query (SMQ) "Hypersensitivity (narrow scope)"

Hypersensitivity reactions: TEAEs in MedDRA SMQ "Hypersensitivity (narrow scope)"

- **Injection site reactions**
  - TEAEs in MedDRA HLT "Injection site reactions" or HLT "Administration site reactions NEC".
- **Hepatic events and drug-induced liver injuries, Drug related hepatic disorders**
  - TEAEs in MedDRA SMQ narrow scope of "Drug related hepatic disorders - comprehensive search (SMQ)" excluding the 2 sub-SMQs of "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)".
- **Malignancies**
  - Malignant or unspecified tumours: TEAEs in MedDRA SMQ "Malignant or unspecified tumours (SMQ)"
  - Malignant tumours: TEAEs in MedDRA SMQ "Malignant tumours (SMQ)"

Note: the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" will be reviewed for potential malignancies.

Should an Adverse Event of Interest has not occurred during the study, the corresponding line should be included with zero occurrences.

The following tables will be created:

- TEAEs of interest by PT, in SS,
- EAIR for TEAEs of interest by PT, in SS (combined Main and Extension Portion among participant received at least one dose Zilucoplan).

5.6.4 Additional Safety Assessments

Further safety assessments include laboratory data, vital signs and 12 Lead ECG. Details of analysis are written further below. All analysis will be based on the SS.

5.6.4.1 Clinical laboratory evaluations

The following table lists all hematology, chemistry, urinalysis and coagulation analytes collected throughout the study, using a central laboratory according to the schedule of the study protocol.

Table 5–1: Laboratory Assessments

Chemistry	Hematology
Alanine aminotransferase (ALT) Albumin	Hematocrit Hemoglobin

Table 5–1: Laboratory Assessments

Chemistry	Hematology
Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Aldolase Blood urea nitrogen (BUN) C-reactive protein (CRP) Calcium Chloride Creatinine Creatine Kinase (CK) Gamma-glutamyl transferase (γ-GT) Glucose Lactate dehydrogenase (LDH) Lipase Potassium Sodium Total bilirubin (TBL) Total protein	Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) White blood cell (WBC) count and differential: Basophils (% and absolute) Eosinophils (% and absolute) Lymphocytes (% and absolute) Monocytes (% and absolute) Neutrophils (% and absolute)
	Coagulation (among participants receiving anticoagulant treatment)
	International normalized ratio (INR)/prothrombin time (PT) Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)
	Urinalysis
	pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, cells and microscopic examination (if necessary).

5.6.4.1.1 Laboratory values over time

All laboratory values listed at Table 5–1 of Section 5.6.4.1 will include on treatment data for analysis defined as the values after the first dose of the study drug until on or before the last dose plus 40 days (or last visit depending which occurs first). At all tables, laboratory assessments will be sorted by panel (chemistry, hematology, coagulation, urinalysis). Within each panel the assessments will be sorted alphabetically.

Summaries on Markedly Abnormal (MA) values will also be provided for the Main portion by scheduled visit and overall (including unscheduled visits) and for the Extension portion by scheduled visit and overall (including unscheduled visits), for each IMP. MA criteria are listed at Section 6.1.7, Table 6–3 MA criteria are defined by Grade 3 or higher events according to the Common Terminology for Adverse Events (CTCAE), Version 5.0, November 17, 2017 unless otherwise noted.

All laboratory test results will be listed, including baseline, scheduled and unscheduled visits with results in standard units. Values outside the reference range for the continuous variables will be flagged in the listings. The reference ranges will also be displayed. In addition, the

listings will include a flag for values identified as MA. Additional lab test for pregnancy testing, will also be listed.

5.6.4.1.2 Individual Subject Changes of Laboratory Values

The laboratory variables that are categorized as normal, high or low based on the reference range as supplied by the analytical laboratory will be presented in shift tables from baseline to each scheduled post-baseline visit by IMP and any post-baseline visit (including unscheduled visits) by IMP.

The number and percentage of participants who meet the criteria with respect to elevated liver function tests and drug-induced liver injuries (PDILI) will be summarized by IMP at each scheduled visit and at any visit (including unscheduled visits), Table 6–4 in Section 6.1.7. A listing will also be provided for participants who meet at least one of the criteria.

5.6.4.2 Vital Signs

The vital signs assessed are the Heart Rate, the Body Temperature and the Systolic and Diastolic Blood Pressure, all in sitting position.

5.6.4.2.1 Vital Sign Values Over Time

Vital signs summaries will only include on treatment data defined as those measurements after the first study treatment dose until the day of the last dose plus 40 days (or last visit depending which occurs first).

Analysis will be performed descriptively for the change from baseline to each post baseline visit by IMP. Change from baseline of each vital sign parameter will be summarized only among participants with both baseline and post baseline values:

Change from Baseline = post Baseline – Baseline value

Summaries of vital sign abnormalities will be created for the Main and Extension portion by scheduled visit and overall (including unscheduled visits) for each IMP. Criteria for vital sign abnormal values are shown in Table 6–5,Section 6.1.7.

A by-participant listing of all vital sign measurements at each visit and change from baseline will be presented by IMP and visit. The listing will include a flag for values identified as abnormal.

5.6.4.2.2 Individual Subject Changes of Vital Sign Values

A by patient listing will be provided (assessing scheduled and unscheduled visits), capturing for each vital sign parameter of the participants with at least one abnormality in the value post-baseline. Results obtained for the vital sign parameters will be displayed.

5.6.4.3 Electrocardiograms

The following assessments will be summarized and reported: PR interval, RR interval, QRS duration, QT interval, QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$).

5.6.4.3.1 Electrocardiogram Values Over Time

ECG summaries will only include on treatment data defined as those measurements after the first study treatment dose and on or before the last dose plus 40 days (or last visit, depending which occurs first).

Analysis will be performed descriptively for the change from baseline to each post baseline visit by IMP. Change from baseline of each ECG parameter, will be summarized only among participants with both baseline and post baseline values:

Change from baseline = post baseline – baseline value

Summaries of ECG abnormalities will be created for the Main and Extension portion by scheduled visit and overall (including unscheduled visits) for each IMP. Criteria for ECG abnormalities values are listed in Table 6–6 in Section 6.1.7.

A by-participant listing of all ECG measurements when performed and change from baseline will be presented by IMP and visit. The listing will include a flag for values identified as based on the abnormality criteria.

5.6.4.3.2 Individual Subject Changes of Electrocardiograms Values

The ECG that are categorized as normal, high or low based on the reference range in shift tables from baseline to each scheduled post-baseline visit by IMP and any post-baseline visit (including unscheduled visits) by IMP.

A by patient listing will be provided (assessing scheduled and unscheduled visits), capturing each or the 12 Lead ECG parameters of the participants with at least one abnormalvalue post-baseline based on the abnormality criteria. Results obtained for the ECG parameters will be displayed.

5.6.4.4 Other safety endpoint(s)

5.6.4.4.1 Physical examination

Any clinically significant abnormalities in physical examination will be reported as AEs when appropriate with reference the period after the first administration of study dose until the last day of study dose administration plus 40 days (or last visit, depending which occurs first).

5.6.4.4.2 Immunogenicity

Blood samples for ADA assessment will be collected prior to dose administration at baseline (screening data will be considered as baseline data for ADA assessments), Day 8, Day 29 and Day 57 as well as Day E8, Day E28, Day E57, Day E117 and every 3 months after, including

final Extension visit in all participants prior to drug administration. These samples will be used to investigate and characterize any ADA response over time in SS.

- Sample values that are either 'negative screen' or 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**
- Samples that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc, will be defined as **Missing**

Sample neutralizing antibody (NAb) status (positive/negative/missing) will be determined for ADA positive samples.

The following ADA classifications will be derived from the sample ADA status:

Table 5–2: ADA Classification

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Participants who are ADA negative at baseline and ADA negative at all sampling points post-baseline.
2	Pre-ADA negative – treatment induced ADA positive	Participants who are ADA negative at baseline and ADA positive at any sampling point post-baseline. It also includes participants who have a missing pre-treatment sample (either missing or insufficient volume) at baseline with one or more ADA positive post-baseline samples.
3	Pre-ADA positive – treatment reduced ADA	Participants who are ADA positive at baseline, and ADA negative at all sampling points post-baseline (including the Extension Portion of the study).
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who are ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Extension Portion) with titer values of the same magnitude as baseline (less than a predefined fold difference from the baseline value which will be defined within the validation of the assay, i.e. minimum significant ratio of the assay).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who are ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Extension Portion) with increased titer values compared to baseline (greater than a predefined fold difference increase from Baseline value which will be defined within the validation of the assay i.e. minimum significant ratio of the assay).

Classification	Classification Label	Definition
6	Inconclusive	Participants who have an ADA positive Baseline sample and some post-Baseline samples are missing, while other post-Baseline samples are ADA negative.
7	Treatment emergent ADA positive	Combination of 2 and 5.
8	Pre-ADA positive	Combination of 3, 4, and 5.

In addition to the ADA classifications above, for the purpose of evaluations of the impact of ADA on plasma concentrations and efficacy and safety endpoints, the following definitions will be used:

- Cumulative ADA status (positive/negative). If a participant had at least one positive sample at any time point up to and including the given time point, that participant will be counted as positive at that time point, regardless of any subsequent negative measurements. Thus, the number of participants included in the summary of positive and negative samples will vary by time point for each IMP.
- Overall ADA status. A participant will be classified as overall ADA Positive if at least one post-baseline measurement is positive. A participant will be classified as overall ADA negative if at all post-Baseline visits the ADA status is Negative.

The ADA of Zilucoplan will be measured using a three-tiered assay approach: screening assay, confirmatory assay and titration assay. Any sample confirmed positive for ADA will be assayed to determine whether there is neutralizing potential.

The following tables will be presented on the SS.

- Number and percentage of participants with positive, negative or missing sample ADA status at the time of each visit and all visits by IMP.
- Number and percentage of participants in each of the ADA classifications presented in Table 5–2 by IMP.
- Number and percentage of participants in each of the NAb classifications presented in Table 5–2 by IMP.
- The prevalence of immunogenicity (Classification 2, 3, 4 and 5), defined as the (cumulative) proportion of participants having ADA positive samples (including pre-ADA positive) at any point up to and including that time point will be summarized by IMP and total. Missing samples will not be included in the denominator.
- The same table will be repeated for Nab (cumulative and overall Nab status will be defined as described above for ADA).
- The first occurrence of treatment-emergent ADA positive will be summarized using frequency and percentage at each post-baseline visit by IMP group. Participants will be counted only once in the numerator based on the earliest visit at which treatment-emergent

ADA positivity is observed. At other visits, participants will be counted in the denominator (assuming a measurement is available). Missing measurements will not be included in the denominator.

- A summary table of all immune related TEAEs by ADA status will be presented by IMP group. For this summary, participants will be presented for TEAEs occurring prior to becoming treatment emergent ADA positive, TEAEs occurring after becoming TE ADA positive and TEAEs for participants who remained TE ADA negative (classifications 1,3,4).
  - Notes: Study physician/safety physician/safety lead will mark the Preferred Term of immune related AEs based on an excel output of all TEAEs (blinded) after database lock. The marked AEs will be used for the summary.

The results for the ADA assessments will be listed by IMP group and timepoint, including the screening assay, confirmatory assay, ADA titer, NAb titer, PK concentration, change from Baseline, treatment-emergent ADA status and ADA classifications. In addition, time since administration of IMP will be reported (in days).

A TEAE overview table will be presented for active treatment by ADA status. Additionally, the number and percentage of participants who experience some AEIs (Hypersensitivity reactions, injection sites reactions as defined in Section 5.6.3 and autoimmune disorders) will be presented by SOC and PT and by ADA Status. Autoimmune disorders will be defined if HLT is in "Autoimmune disorders". For these summaries, participants will be presented for TEAEs occurring prior to becoming treatment emergent ADA positive, TEAEs occurring after becoming treatment emergent ADA positive, and TEAEs for participants who remained TE ADA negative (classifications 1,3,4,6).

5.7 Other Analyses

5.7.1 Other endpoints and/or parameters

5.7.1.1 Pharmacokinetics

The plasma concentrations of Zilucoplan and its two major metabolites ([redacted]) will be summarized by IMP and by scheduled sampling day for the PK-PPS using n, arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric coefficient of variation (geoCV) and 95% CI (assuming log-normally distributed data).

A spaghetti plot of combined individual concentration versus time profiles will be presented by analyte in linear and semi-logarithmic scale with all participants overlaid on the same plot.

Additionally, Mean (+SD) plasma concentration versus time overlaid for both analytes will also be presented for all scheduled timepoints on a linear and semi-logarithmic scale. The SD will not be provided on the semi-logarithmic scale.

All figures will include the lower limit of quantification (LLOQ) on the semi-logarithmic plots.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as below the limit of quantification (BLQ)

- Descriptive statistics of concentrations will be calculated if at most 1/3 of the individual data points at a timepoint are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance.
- The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geoCV) is 0
- The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data

$$\text{geoCV}(\%) = \sqrt{\exp\left(\text{SD}^2\right) - 1} \times 100.$$

Individual concentrations will be listed by IMP for the PK-PPS and will include the actual sampling time in days relative to the previous dose the ADA titer observed for the binding assay and the NAb titer for the same visit and CK change from baseline for the corresponding visit.

Summary statistics (mean, SD, median, minimum, maximum, geometric mean and geometric CV%) will be produced for each PK parameter for each analyte.

The results of the PK will be reported separately from the main clinical study report analyses and therefore analysis will not be stated at the current document.

Plasma concentration data of Zilucoplan may be subject to population pharmacokinetic analysis to derive population estimates of PK parameters and test the effect of various covariates such as anti-drug antibodies, age, weight, gender. Details of the analysis will be described separately. This analysis may be performed by combining the data from the current study with data from other Zilucoplan studies, if deemed appropriate. The results of the population PK analysis will not be reported in the study CSR but in a separate modeling report.

5.7.1.2 Pharmacodynamics

Pharmacodynamic analyses will be performed on the PD-PPS. The pharmacodynamic endpoints include sRBC lysis assay and C5 levels.

Summary statistics based on observed data will be provided for the values, change from baseline, and percent change from baseline at each of the scheduled assessment time point.

The change from baseline for each of these endpoints will be assessed by an ANCOVA model with treatment as a factor and the corresponding baseline value as covariate. The active dose will be compared to the placebo group based on the ANCOVA model; corresponding 90%CIs will be produced.

Population PD or population PK/PD analyses may be conducted for the PD variables of interest. Details of such PD or PK/PD analyses will be described separately. The results of the analyses will not be reported in the study CSR but in a separate modeling report.

5.8 Subgroup Analyses

The primary and continuous secondary efficacy endpoints will be summarized in ITT for the Main Portion of the study, based on the following subgroups:

- Sex (male, female)
- Age:<55 years, ≥55 years
- Stratification factor: anti-HMGCR / anti-SRP groups (positive / negative, negative / positive)

  Note: The stratification factor in the subgroup analysis will be based on the values entered into the IWRS at randomization.

The associated estimand for the subgroup analysis is defined as:

- Treatment: Zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population in the specific subgroup
- Endpoints:
  - Percentage change from baseline to Week 4 and Week 8 in CK levels;
  - At least minimal response based on (ACR/EULAR) Response Criteria Scale at Week 4 and Week 8;
  - Change from baseline to Week 4 and Week 8 in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only);
  - Change from baseline to Week 4 and Week 8 in Proximal Manual Muscle Testing (MMT);
  - Change from Baseline to Week 4 and Week 8 in Physician Global Activity Visual Analogue Scale (VAS);
  - Change from baseline to Week 4 and Week 8 in Health Assessment Questionnaire (HAQ);
  - Change from baseline to Week 4 and Week 8 in MDAAT Extramuscular Disease Activity VAS Score;
  - Change from Baseline to Week 4 and Week 8 in FACIT-Fatigue Scale;
- Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after prohibited medication;
- Population level summary:
  - Continuous endpoints: mean change from baseline
  - Proportion of patients achieving at least minimal ACR/EULAR response

Analysis will be based only on descriptive statistics (no hypothesis testing).

5.9 Interim Analyses

No interim analysis is planned for the Main Portion of the study.

Interim analyses of the Extension Portion of the study, after Week 8 of the Main Portion of the study has been locked and unblinded, may be performed.

5.10 Data Monitoring Committee (DMC) or Other Review Board

The safety of study participants is monitored throughout the study on an ongoing basis. Given the double blind, placebo-controlled design of the study, this standard safety data review is performed while blinded to treatment assignment. If an unblinded data review should become necessary to ensure subject safety, a separate DMC will convene and evaluate study data as appropriate. To ensure the scientific integrity of the study, members of the DMC are not be directly involved in management of the study.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

A separate table on demographics and baseline characteristics based on the ITT_{EXT} will be created.

- Age (years), calculated as (informed consent date – date of birth + 1)/365.25.

  If day and month are missing from the date of birth, impute January 1st; if only the day is missing then impute the 1st.
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) calculated as: BMI= "Weight (kg)" / ("Height (m)")^2 using the weight and height measurements obtained at screening.
- Sex (Male/Female)
- Racial Group (American Indian /Alaska native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Years of Age (≤18, >18 - < 55, ≥55 - < 65, ≥ 65).
- Weight in Kg (<56, 56-<77, ≥ 77 - <150, ≥ 150)
- BMI in kg/m^2 (<18.5, 18.5 - <25, ≥25 - <30, ≥30 - >40, ≥ 40)
- Ambulatory participant (yes, no)
- Geographic region (North America, Europe)
- Countries (country 1, country2, etc.)
- Months since initial diagnosis calculated as:

$$\text{Months since diagnosis} = \frac{(\text{Date of randomization} - \text{Date of Initial IMNM Diagnosis}^{1} + 1)}{30.5}.$$

[1]If the date of initial IMNM diagnosis is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or the last day of the year if day and month are missing). Note that if the date of randomization is missing then the duration of disease will be derived using the date of screening.

- Age in years at initial diagnosis calculated as: Year of Initial IMNM Diagnosis − Year of Birth
- HMGCR SRP Antibodies (positive/negative, positive/negative),
- Muscle Biopsy performed (yes, no),
  - normal muscle biopsy
  - necrotic muscle fibers observed
  - complement C5b-9 or C9 staining performed
  - complement C5b-9 or C9 staining positive
  - complement C5b-9 or C9 staining negative
- Electromyography performed (yes, no)
  - normal electromyography
  - increased insertional activity and spontaneous fibrillations
  - abnormal myopathic low-amplitude, short-duration polyphasic motor unit potential
  - complex repetitive discharges
  - other
- MRI performed (yes, no)
  - normal MRI
  - muscle edema
  - muscle inflammation
  - muscle fibrosis
  - other
- Extramuscular Manifestations of IMNM (yes, no)
  - skin
  - cardiac
  - skeletal
  - gastrointestinal
  - pulmonary

  - constitutional
- History of any statin use (yes, no)
  - Atorvastatin
  - Fluvastatin
  - Lovastatin
  - Pravastatin
  - Pitavastatin
  - Simvastatin
  - Rosuvstatin
  - other

6.1.2 Protocol deviations

A listing of all protocol deviations will be provided based on the ITT and presented by IMP, indicating if PD is COVID-19 related or not.

6.1.3 Medical history

Any medical condition reported on the Medical History form of the eCRF will be coded based on MedDRA dictionary. Medical History will be summarized by IMP and overall, by Primary System Organ Class (PSOC) and preferred term (PT) in the ITT. A participant will be counted only once for each PT. If a participant reports multiple PTs within the same PSOC then the participant will be counted only once for this PSOC. The summary will present the results alphabetically by PSOC and within each PSOC by decreasing frequency of the PT based on the active comparator. Summaries will be repeated by pre and during the COVID-19 era based on the enrollment date.

A by-participant listing will be provided based on the ITT population. IMNM medical history will be listed separately in ITT as it is part of the baseline clinical characteristic.

6.1.4 Prior/concomitant Medications

6.1.4.1 Prior and Concomitant Medications (non – IMNM related)

Prior and concomitant medications (prescriptions or over-the-counter medications) as recorded in the eCRF will be summarized on tables overall by IMPs in SS.

A non – IMNM related medication is defined by the “indication” value on the Prior and Concomitant Medication eCRF form not equal to “Therapy for IMNM”.

Medications will be classified as follows based on imputed start and stop dates / times as outlined in Section 5.1.1.8.

- **Past** medications will include any medications that started and stopped before the first administration of study drug.
- **Prior** medications will include any medications that started before the first administration of study drug.
- **Baseline** medications will include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).
- **Concomitant** medications will include any medications that have been taken at least once after the first administration of study drug during the Main or the Extension Period.
- **Concomitant Only** medications will include any medication that started after the first administration of study drug and continues during the Main or the Extension Period. Any medication with a start date on the first dosing date and time unknown, will be assumed to be concomitant only.

Medications will be presented in alphabetical order by Anatomical Main Group (ATC Level 1), then by Pharmacological Subgroup (ATC level 3) and finally by decreasing frequency of PT within Zilucoplan group. In the case of ties, sort these alphabetically within the Zilucoplan. Summaries will include the overall number and percentage of participants receiving at least one treatment of a PT.

6.1.4.2 Prior and concomitant Medications (IMNM related)

IMNM specific medication will be presented separately from the other prior and concomitant medications (for both tables and listings). An IMNM specific medication is defined by the "indication" value on the Prior and Concomitant Medication eCRF form ="Therapy for IMNM".

The following tables summarizing the IMNM medications received will be created based on the SS:

- **Past IMNM** medications will include any IMNM medication that started and stopped before the first administration of study drug.
- **Prior IMNM** medications will include any IMNM medication that started before the first administration of study drug.
- **Baseline IMNM** medications will include any IMNM medication that started prior to dosing and continued after (classified as prior and concomitant IMNM medications).
- **Concomitant IMNM** medications will include any IMNM medication that have been taken at least once after the first administration of study drug during the Main or the Extension Period.

Where an IMNM medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or taken at baseline, it will be assumed that it is taken at baseline. Of note, an IMNM medication may be considered in both of these categories.

- Additionally, the number and percentage of participants who have ever received one or more of the IMNM specific medications presented below will be summarized accordingly (eCRF form = "IMNM Treatment History":Prednisone for IMNM (yes/no)

- Azathioprine for IMNM (yes/no)
- Mycophenolate mofetil for IMNM (yes/no)
- Cyclosporine for IMNM (yes/no)
- Cyclophosphamide for IMNM (yes/no)
- Methotrexate for IMNM (yes/no)
- Tacrolimus for IMNM (yes/no)
- Rituximab for IMNM (yes/no) and number of cycles the past 24 months (continuous)
- Plasma Exchange for IMNM (yes/no) and number of cycles the past 24 months (continuous)
- IVIG for IMNM (yes/no) and number of cycles the past 24 months (continuous)
- scIG for IMNM (yes/no) and number of cycles the past 24 months (continuous)
- Other (yes/no)

6.1.5 Data derivation rules

6.1.5.1 Triple timed up and go test

The triple timed up and go test (3TUG) is a non-invasive and reproducible measure, which measures clinically important muscle weakness that impairs participant's ability to walk, climb stairs and stand up from a chair. The test will only be performed in participants who are ambulatory. The 3TUG test involves the participant getting up from a seated position in a chair, walking at their normal pace for 3 meters, turning around, walking back to the chair, and sitting down. This sequence is repeated 3 times without rest. Sites will record each lap time rounded to the nearest second, and the 3TUG time is the average of the 3 lap times. The average of the 3 lap times will be calculated to the nearest tenth place (Sanders, et al. 2018). If 2 or more of the lap times are missing, the 3TUG time will be set to missing.

6.1.5.2 Proximal Manual Muscle Testing

The proximal manual muscle testing (MMT) assesses muscle strength using manual muscle testing in 7 muscle groups. A zero to 10-point scale based on standard MMT grades will be used of 7 proximal, distal, and axial muscles (Kendall et al. 1993; Rider, Koziol, et al. 2010).

The 7 muscle groups are:

1. Trapezius
2. Deltoid middle
3. Biceps brachii
4. Gluteus maximus
5. Gluteus medius
6. Iliopsoas

7. Quadriceps.

The total score is the sum of the 7 muscle group scores with a range of 0−140 (i.e., each of the 7 muscle groups are scored on the left and right sides on a 0−10 point scale) with a higher score indicating higher muscle strength. If any of the individual items are missing the total score will be set to missing.

6.1.5.3 Physician Global Activity Visual Analogue Scale

The Physician Global Activity visual analogue scale (VAS) score, measures the global evaluation by the treating physician of the overall disease activity of the patient at the time of assessment using a 10 cm visual analogue scale (with a lower score indicating less disease activity and a higher score indicating greater disease activity) and a 0-4 point disease activity scale with 0=none and 4=extremely severe activity (Rider, Werth, et al. 2011). The VAS score will be the number of centimeters rounded to the nearest tenths place.

6.1.5.4 Patient Global Activity Visual Analogue Scale

The Patient Global Activity VAS score measures the global evaluation by the patient of the patient's overall disease activity at the time of assessment using a 10 cm visual analogue scale with a lower score indicating less disease activity and a higher score indicating greater disease activity (Rider, Werth, et al. 2011). The score will be the number of centimeters rounded to the nearest tenths place.

6.1.5.5 Health Assessment Questionnaire (HAQ)

The HAQ is a participant related outcome measure that assesses physical function.

There are 8 sections:

1. Dressing and Grooming
2. Arising
3. Eating
4. Walking
5. Hygiene
6. Reach
7. Grip
8. Activities

There are 2 or 3 questions for each section. Scoring within each section is based on the following response scales:

- Without ANY difficulty = 0
- With SOME difficulty = 1

- With MUCH difficulty =2
- UNABLE to do =3
- Answer Missing
- Answer Ambiguous

For each of the 8 sections, the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for the section is 2.

In addition, if an aide or device is used or if help is required from another individual, then the minimum score for that section is 2 (note: questions regarding aids or devices are requested after the Walking and Activities items).

If the section score is already 2 or more then no modification is made.

If a component question is left blank (i.e., "Answer Missing") or the response is too ambiguous (i.e., "Answer Ambiguous") to assign a score, then the score for that category is determined by the remaining completed question(s).

A HAQ overall score is calculated using by summing the 8 scores (i.e., from the 8 sections) and dividing by 8. In the event that one section is not completed by a subject, the summed score would be divided by 7. If more than one section is not completed the summed score would be set to missing.

6.1.5.6 Myositis Disease Activity Assessment Tool (MDAAT)

The MDAAT measures the degree of disease activity of extra-muscular organ systems and muscle. This is a combined tool that includes the myositis disease activity assessment visual analogue scales (MYOACT), which is a series of physician's assessments of disease activity of various organ systems modified from the Vasculitis Activity Index (Whiting-O'Keefe, Stone and Hellmann 1999), and the Myositis Intention to Treat Activity Index (MITAX).

The following ten MDAAT 0-10 VAS Scores will be summarized with descriptive statistics for each IMP:

1. Constitutional Disease Activity
2. Cutaneous Disease Activity
3. Skeletal Disease Activity
4. Gastrointestinal Disease Activity
5. Pulmonary Disease Activity
6. Cardiovascular Disease Activity
7. Other Disease Activity
8. Extramusular Disease Activity (note: this is the secondary efficacy endpoint: MDAAT Score).
9. Muscle Disease Activity

10. Global Disease Activity

The following MDDAAT items are scored on a 0 - 4 scale (or NA), based on worsening or improvement in specific clinical features, as described below.

- 0 = Not present in the last 4 weeks
- 1 = Improving - clinically significant improvement in the last 4 weeks compared to the previous 4 weeks
- 2= The same - manifestations that have been present for the last 4 weeks without significant improvement or deterioration compared to the previous 4 weeks
- 3= Worse - clinically significant deterioration over the last 4 weeks compared to the previous 4 weeks
- 4= New - in the last 4 weeks (compared to the previous 4 weeks)
- NA = Cannot be assessed

The following are the set of MDAAT items scored using this 0-4 (NA) scale:

- Pyrexia – documented fever > 38o Celsius
- Weight loss – unintentional > 5%
- Fatigue / malaise / lethargy
- Cutaneous ulceration
- Erythroderma
- Panniculitis
- Erythematous rashes: **a. with secondary changes (e.g. accompanied by erosions, vesiculobullous change or necrosis)**
- Erythematous rashes: Alopecia: **b. Focal, patchy with erythema**
- Heliotrope rash
- Gottron's papules / sign
- Periungual capillary changes
- Alopecia: **a. Diffuse hair loss**
- Alopecia: **b. Focal, patchy with erythema**
- Mechanics hands
- Arthritis: **a. Severe active polyarthritis**
- Arthritis: **b. Moderately active arthritis**
- Arthritis: **c. Mild arthritis**
- Arthralgia Dysphagia: **a. Moderate / severe dysphagia**
- Dysphagia: **b. Mild dysphagia**

- Abdominal pain related to the myositis disease process: **a. Severe**
- Abdominal pain related to the myositis disease process: **b. Moderate**
- Abdominal pain related to the myositis disease process: **c. Mild**
- Respiratory muscle weakness without interstitial lung disease (ILD): **a. Dyspnea at rest**
- Respiratory muscle weakness without interstitial lung disease (ILD): **b. Dyspnea on exertion**
- Active reversible ILD (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): **a. Dyspnea or cough due to ILD**
- Active reversible ILD (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): **b. Parenchymal abnormalities on chest x-ray or high resolution CT scan (HRCT) and / or ground glass shadowing on HRCT**
- Active reversible ILD (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): c. Pulmonary Function Tests: > 10% change in FVC OR > 15% change in DLCO
- Dysphonia: **a. Moderate to severe**
- Dysphonia: **b. Mild**
- Pericarditis
- Myocarditis
- Arrhythmia: **a. Severe arrhythmia**
- Arrhythmia: **b. Other arrhythmia, except sinus tachycardia**
- Sinus tachycardia
- Other Myositis: **a. Severe muscle inflammation**
- Myositis: **b. Moderate muscle inflammation**
- Myositis: **c. Mild muscle inflammation**
- Myalgia

6.1.5.7 ACR/EULAR Response Criteria

The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) scale was created to develop a response criterion for patients with myopathy. The scale utilizes a conjoint analysis-based continuous model using absolute percent change in core set measures (physician, patient, and MDAAT; muscle strength; Health Assessment Questionnaire; and muscle enzyme levels). A total improvement score (range 0-100) is determined by summing scores for each core set measure and comparing improvement in each respective core set measure. Thresholds for minimal, moderate, and major improvement are ≥20, ≥40, and ≥60 points in the total improvement score (Aggarwal, et al. 2017). The total improvement score will be calculated based on the core set measures as recorded in the eCRF and from central laboratory results as defined below in the following table.

Table 6–1: ACR/EULAR Response Criteria

Six Item with Improvement Score Scales			
1: Physician global activity	**Improvement Score**	**4: Health Assessment Questionnaire**	**Improvement Score**
From the Physician Global Activity Visual Analogue Scale		From the Health Assessment Questionnaire	
Worsening to 5% improvement	0	Worsening to 5% improvement	0
>5–15% improvement	7.5	>5–15% improvement	5
>15–25% improvement	15	>15–25% improvement	7.5
>25–40% improvement	17.5	>25–40% improvement	7.5
>40% improvement	20	>40% improvement	10
2: Patient global activity		**5: Enzyme[a] (most abnormal)**	
From the Patient Global Activity VAS		From the clinical laboratory data	
Worsening to 5% improvement	0	Worsening to 5% improvement	0
>5–15% improvement	2.5	>5–15% improvement	2.5
>15–25% improvement	5	>15–25% improvement	5
>25–40% improvement	7.5	>25–40% improvement	7.5
>40% improvement	10	>40% improvement	7.5
3: Manual muscle testing		**6: Extramuscular Disease Activity**	
From the Proximal Manual Muscle Testing		From the Extramuscular Disease Activity VAS component of the MDAAT	
Worsening to 2% improvement	0	Worsening to 5% improvement	0
>2-10% improvement	10	>5–15% improvement	7.5
>10–20% improvement	20	>15–25% improvement	12.5
>20–30% improvement	27.5	>25–40% improvement	15
>30% improvement	32.5	>40% improvement	20
Note: this table is from Table 3 in Aggarwal, et al. (2017).			

[a] For muscle enzymes, the most abnormal serum muscle enzyme value at baseline (creatine kinase, aldolase, alanine transaminase, aspartate aminotransferase, lactate dehydrogenase) is used to determine % improvement. Most abnormal will be defined as enzyme with the highest % above the ULN.

The total improvement score is the sum of all 6 improvement scores associated with the change in each core set measure. The score is between 0 and 100 corresponds to the degree of improvement, with higher scores corresponding to a greater degree of improvement.

A total improvement score of ≥20 represents minimal improvement, a score of ≥40 represents moderate improvement, and a score of ≥60 represents major improvement.

6.1.5.8 FACIT-Fatigue Scale

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale is a 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the preceding week. The level of fatigue is measured on a five point ordinal scale (4 = not at all fatigued to 0 = very much fatigued) (Webster, Cella and Yost 2003). The items of the FACIT-Fatigue Scale are given in the table below.

[redacted]

Note that for the analyses, FACIT values coded as "ambiguous" are mapped to "missing" category.

6.1.6 AEs of Special Interest

Not applicable.

6.1.7 Markedly Abnormal (MA) Criteria for Safety Endpoints

Criteria listed in Table 6–3 will be applied for the determination of MA values in laboratory parameters. They are based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5, November 17, 2017. The MA criterion is defined as the incidence of at least Grade 3 CTCAE, unless otherwise noted.

If both high and low criteria are shown for a parameter, then criteria should be summarized separately in tabular summaries.

Table 6–3: CTCAE v5.0 grades for laboratory assessments to be analyzed

Parameter	Unit (conventional)	Unit (Standard)	Marked Abnormality Criteria
Hemoglobin	g/dL	g/L	< 8.0 g/dL; <80g/L
WBC (Leukocytes)	10^9/L	10^9/L	Low: <2.0 x 10^9/L; High: >100 x 10^9/L
Lymphocytes Absolute	10^9/L	10^9/L	Low: <0.5 x 10^9/L High>20 x 10^9/L
Neutrophils Absolute	10^9/L	10^9/L	<1.0 x 10^9/L
Platelets	10^9/L	10^9/L	<50.0 x 10^9/L
AST	U/L	U/L	>5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal
ALT	U/L	U/L	>5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal
ALP	U/L	U/L	5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal
γ-GT	U/L	U/L	>5.0xULN if Baseline value is normal; > 5.0x Baseline value if Baseline is abnormal
TBL	mg/dL	µmol/L	>3.0xULN if baseline value is normal > 3.0xbaseline value if baseline is abnormal
Albumin	g/dL	g/L	<2g/dL; <20g/L
Creatinine	mg/dL	µmol/L	>3.0x ULN
CRP[a]	mg/dL	mg/L	>10mg/dL >100 mg/L

Table 6–3: CTCAE v5.0 grades for laboratory assessments to be analyzed			
Parameter	**Unit (conventional)**	**Unit (Standard)**	**Marked Abnormality Criteria**
Corrected Calcium (Ca)[b]	mg/dL	mmol/L	High: Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L Low: Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L
Potassium	mEq/L	mmol/L	Low: <3.0 mmol/L High: > 6.0 mmol/L
Sodium	mEq/L	mmol/L	Low: <125 mmol/L High: >155 mmol/L
Glucose[c]	mg/dL	mmol/L	Low: <40mg/dL; < 2.2 mmol/L High: >250 mg/dL; >13.9 mmol/L
eGFR[d]	mL/min/1.73 m^2	mL/min/1.73 m^2	eGFR <29 mL/min/1.73 m^2

[a] Includes CRP and High Sensitivity (HS) CRP. Reference for marked abnormality criteria: Nehring, S.M.; Goyal, A.; Patel, B.C. (2020). StatPearls Publishing, web link: https://www.ncbi.nlm.nih.gov/books/NBK441843/

[b] Corrected Ca (mg/dl) = Ca (mg/dl) + (0.8 [4 - measured albumin (g/dl)]); Corrected Ca = [0.8 x (normal albumin - patient's albumin)] + serum Ca, Karbhari, D.S.; Karbhari, S.; Karbhari, N.S.; Patel, S. (2017).

[c] Glucose high criterion defined by Grade 3 and higher events according to CTCAE, Version 4.03, June 14, 2010

[d] GFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration or CKD-EPI formula (https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi) which is eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. For derivation from values in standard units (umol/L) the κ values are 61.9 for females and 79.6 for males.

The table for the markedly abnormal liver function tests will contain data beyond the CTCAE v5.0 Grade 3 thresholds as outlined in Table 6–4 above, in order to allow for a more thorough review of elevated liver function tests.

There will be one table by IMP in the SS, which will display the count and percentage of participants meeting the criteria mentioned in Table 6–4 at any visit during the study (including unscheduled visits). For the combined criteria to be fulfilled the conditions should be present in the same visit.

The liver function results for study participants with markedly abnormal criteria will be listed for all study visits (that is including the not on treatment assessments).

Table 6–4: Markedly Abnormal Criteria for Liver Function Tests

Category	Parameter	Criterion[a]
Drug Hepatic disorders TEAEs	TEAEs in MedDRA SMQ	"Drug related hepatic disorders - comprehensive search (SMQ-narrow scope)" *excluding the 2 sub-SMQs of "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)"*
Elevated Liver Function Tests	AST	>3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
	ALT	>3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
	AST or ALT	>3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
	TBL	>1.5 x ULN, >2 x ULN
	ALP	1.5 x ULN
Potential drug-induced liver injury (DILI) criteria	AST or ALT	>3xULN with TBL >1.5xULN
	AST or ALT	>3xULN with TBL >2xULN
	Hy's Law	AST or ALT > 3×ULN with concurrent ALP < 2 × ULN and concurrent TBL > 2×ULN

[a] Meeting the criteria at any post-baseline visit after the first infusion of study medication and within 40-days of the last injection and not meeting the same criteria during baseline

Criteria listed in Table 6–5 will be applied in the determination of PCSA (Potentially Clinically Significant Abnormalities) in vital signs of the study participants.

Table 6–5: Abnormality Criteria in Vital Signs

Parameter	Criterion[a]
Systolic Blood Pressure (mmHg)	≤ 90 mmHg and a decrease from Baseline of ≥20 mmHg ≥ 160 mmHg and an increase from Baseline of ≥20 mmHg
Diastolic Blood Pressure (mmHg)	≤50 mmHg and a decrease from Baseline of ≥15 mmHg ≥105 mmHg and an increase from Baseline of ≥ 15 mmHg
Pulse rate (bpm)	≤50 mmHg and a decrease from Baseline of ≥15 mmHg ≥120 mmHg and an increase from Baseline of ≥15 mmHg

[a] Meeting the criteria at any post-baseline visit after the first infusion of study medication and within 40-days of the last injection and not meeting the same criteria during baseline

Criteria listed in Table 6–6 will be applied in the determination of abnormalities in ECG of the study participants.

Table 6–6: Abnormality Criteria in ECG

Parameter	Criterion[a]
QT interval (ms)	≥500ms; ≥60ms increase from Baseline

Parameter	Criterion[a]
QTc(F) (ms)	≥500ms; ≥60ms increase from Baseline
PR interval (ms)	Treatment-emergent value >200ms
QRS interval (ms)	Treatment-emergent value >100ms
Heart Rate (bpm)	<50bpm; >120bpm

[a] Meeting the criteria at any post-baseline visit after the first infusion of study medication and within 40-days of the last injection and not meeting the same criteria during baseline

6.1.8 Compliance

Not Applicable. The number of doses missed will be recorded as detailed in Section 5.6.1.

6.2 Appendix 2: MedDRA Algorithmic Approach to Anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts:

- A narrow search containing PTs that represent core anaphylactic reaction terms:

Preferred Terms:

- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactic transfusion reaction
- Anaphylactoid reaction
- Anaphylactoid shock
- Circulatory collapse
- Dialysis membrane reaction
- Kounis syndrome
- Shock
- Shock symptom
- Type I hypersensitivity

- A broad search that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C or D:

Category B Preferred Terms:

- Acute respiratory failure
- Asthma

- Bronchial oedema
- Bronchospasm
- Cardio-respiratory distress
- Chest discomfort
- Choking
- Choking Sensation
- Circumoral oedemia
- Cough
- Cyanosis
- Dyspnoea
- Hyperventilation
- Irregular Breathing
- Laryngeal dyspnea
- Laryngeal oedema
- Laryngospasm
- Laryngotracheal oedema
- Mouth swelling
- Nasal obstruction
- Oedema mouth
- Oropharyngeal spasm
- Oropharyngeal swelling
- Respiratory arrest
- Respiratory distress
- Respiratory dyskinesia
- Respiratory failure
- Reversible airways obstruction
- Sensation of foreign body
- Sneezing
- Stridor
- Swollen tongue
- Tachypnoea

- Throat tightness
- Tongue oedema
- Tracheal obstruction
- Tracheal oedema
- Upper airway obstruction
- Wheezing.

Category C Preferred Terms:

- Allergic oedema
- Angioedema
- Erythema
- Eye oedema
- Eye pruritus
- Eye swelling
- Eyelid oedema
- Face oedema
- Flushing
- Generalised erythema
- Injection site urticaria
- Lip oedema
- Lip swelling
- Nodular rash
- Ocular hyperaemia
- Oedema
- Periorbital oedema
- Pruritus
- Pruritus allergic
- Pruritus generalized
- Rash
- Rash erythematous
- Rash generalized

- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Urticaria
- Urticaria papular

Category D Preferred Terms:

- Blood Pressure decreased
- Blood Pressure diastolic decreased
- Blood Pressure systolic decreased
- Cardiac arrest
- Cardio-respiratory arrest
- Cardiovascular insufficiency
- Diastolic hypotension
- Hypotension

- An algorithmic approach which combines anaphylactic reaction symptoms in order to increase specificity. A potential anaphylactic reaction is defined as meeting at least one of the following criteria:
  - A narrow term or a term from Category A;
  - A term from Category B - (Upper Airway/Respiratory) AND a term from Category C - (Angioedema/Urticaria/Pruritus/Flush), when both TEAEs occur on two consecutive days, under the condition that Zilucoplan treatment is still ongoing at the first of these two days (both TEAEs will be flagged as anaphylactic reactions)
  - A term from Category D - (Cardiovascular/Hypotension) AND [a term from Category B - (Upper Airway/Respiratory) OR a term from Category C - (Angioedema/Urticaria/ Pruritus/Flush)], when both TEAEs occur on two consecutive days, under the condition that Zilucoplan treatment is still ongoing at the first of these two days (both TEAEs will be flagged as anaphylactic reactions)

6.3 Appendix 2: Changes to Protocol-Planned Analyses

No changes as per study protocol amendment 2, 16 February 2021.

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