TITLE PAGE

STATISTICAL ANALYSIS PLAN

Final Analysis of the Randomized Controlled Period for Part A

Version Number: 1.0

Protocol Title: A Phase 2/3, Double-blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants with Dermatomyositis

Protocol Number: ALXN1210-DM-310

Compound: Ravulizumab (ALXN1210)

Brief Title: Ravulizumab Versus Placebo in Adult Participants With Dermatomyositis

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TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan for ALXN1210-DM-310 is based on Protocol Amendment 3.0, dated 23 Jun 2023.

SAP Version	Version Date	Change	Rationale
1.0	20-August-2023	Not applicable	Original version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic therapeutic class
CDA-IGA	Cutaneous Dermatomyositis Activity Physician's Global Assessment
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CI	confidence interval
COVID-19	coronavirus disease 2019
CSM	core set measures
CST	Chair Stand Test
CW	clinical worsening
DM	dermatomyositis
DPP	Data Presentation Plan
ECG	electrocardiogram
EQ-5D-5L	European Quality of Life Health 5-item questionnaire dimensions 5 level
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
HAQ	Health Assessment Questionnaire
HHD	handheld dynamometry
HR-QoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
IE	intercurrent event
IMACS	International Myositis Assessment and Clinical Group
IMACS-TIS	International Myositis Assessment and Clinical Group - Total Improvement Score
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	least square
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMT	manual muscle testing
NAb	neutralizing antibody
OLE	Open-Label Extension
PCS	physical component summary
PD	pharmacodynamics
PDAS	Pharmacodynamic Analysis Set
PK	pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PROMIS	Patient-Reported Outcomes Measurement Instrument System
PT	Preferred Term
QIC	Quasi-likelihood information criterion
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RCP	Randomized Controlled Period
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SAS	Statistical Analysis Software
SF-36	Short Form Health Survey (36 Questions Version)
SOC	System Organ Class
SS	Safety Set
TEAE	treatment-emergent adverse event
TIS	Total Improvement Score
ULN	upper limit of normal
VAS	visual analog scale

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for Part A of Study ALXN1210-DM-310 Protocol Amendment 3.0, "A Phase 2/3, Double-blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Dermatomyositis." Standard data presentation instructions and table, figure, and listing specifications are contained in the Data Presentation Plan (DPP) in a separate document. The statistical methods for analyses of Part B will each be described in separate SAPs and associated DPPs.

The objective of Part A is to evaluate the efficacy and safety of ravulizumab compared with placebo after 26 weeks.

The primary efficacy analysis of Part A will be performed when the last participant in Part A completes the Week 26 Visit to conduct the analyses of the double-blind Randomized Controlled Period (RCP). At the time of the primary efficacy analysis, the Sponsor will be unblinded. Additional follow-up data for participants who have entered the Open-Label Extension (OLE) Period may be summarized, as relevant.

Changes to the protocol-planned analyses are described in Section 4.10.

1.1. Objectives, Endpoints, and Estimands

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the effect of ravulizumab compared with placebo in the treatment of DM based on improvement in Total Improvement Score (TIS) IMAC-TIS	• TIS40 response at Week 26
Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on improvement in efficacy endpoints	• TIS at Week 26 • Change from Baseline in CDASI Activity Score at Week 26 • Change from Baseline in 5 IMACS core set measures (extramuscular disease activity based on MDAAT, physician global activity assessment, patient global activity assessment, MMT-8, HAQ) at Week 26 • Response related to muscle enzymes: ○ normalization of most abnormal Baseline enzyme at Week 26 • CDASI response (7-point improvement from baseline) at Week 26 • CDA-IGA response (almost clear or clear) at Week 26 • TIS20 response at Week 26 • TIS60 response at Week 26 • Time to first response of TIS20, TIS40, or TIS60, respectively

Table 1: Objectives and Endpoints

Objectives	Endpoints
	• Clinical worsening during RCP at 2 consecutive visits • Receipt of acute therapy with standard DM treatment
Safety	
To characterize the overall safety of ravulizumab in participants with DM	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study intervention discontinuation
PK/PD/Immunogenicity	
To characterize the PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentrations over the study duration • Change in serum free and total C5 concentrations over the study duration • Incidence and titer of ADA over the study duration
Exploratory	
To evaluate the effect of ravulizumab on overall health-related quality of life (HR-QoL) and participant-centered and participant-reported outcomes in DM	• Change from Baseline in EQ-5D-5L at Week 26 • Change from Baseline in PROMIS-29 v2.1 domains at Week 26 • Change from Baseline in SF-36 at Week 26 • Change from Baseline of DM symptoms captured in DM-DSQ at Week 26 • Change from Baseline in Patient Self-Assessment of Disease Activity (last question in the DM-DSQ) at Week 26
To evaluate, complement, inflammatory, autoimmune, and other soluble biomarkers in adult participants with DM	• Presence of myositis-specific autoantibodies (eg, anti-MDA5, anti-NXP2/MJ, and anti-synthetase/Jo-1, anti-TIF1) in blood, and change from Baseline in specific autoantibody/autoantibodies titer over the course of the study • Change from Baseline in plasma complement activation (eg, sC5b-9, etc) over the course of the study • Change from Baseline in serum inflammatory markers (eg, IL6, etc) and other soluble markers (eg, KL6, etc) over the course of the study
To assess the efficacy of ravulizumab in the treatment of DM based on other efficacy endpoints	• Change from Baseline using scale to measure pruritus (5D-itch scale) at Week 26 • Incidence of protocol-defined clinical worsening during RCP • Change from Baseline in handheld dynamometry performance at Week 26 • Change from Baseline in 30-second Chair Stand Test (30s CST) at Week 26 • Change from Baseline in FACIT-Fatigue at Week 26

Primary Estimand

The estimand is described by the following attributes:

- Population: Adult dermatomyositis (DM) participants who have an inadequate response or are intolerant to at least 1 DM treatment
- Endpoint: TIS40 response at Week 26
- Treatment: Ravulizumab versus Placebo
- Intercurrent events (IEs): Receipt of acute therapy with standard DM treatment or prohibited medications, and discontinuation of study intervention due to an AE or lack of efficacy or death during the RCP
  - Such IEs will be addressed via a composite strategy, where participants will be assumed to be TIS40 nonresponders (regardless of the observed TIS value) at all timepoints after first occurrence of either (1) receipt of acute therapy with standard DM treatment and/or prohibited medication, or (2) discontinuation of study intervention due to an AE or lack of efficacy or death
- Population-level summary: Difference in the percentage of TIS40 response between the ravulizumab and placebo arms

1.2. Study Design

Study ALXN1210-DM-310 is a Phase 2/3, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ravulizumab in adult participants with DM. The Phase 2 portion of the study is labeled as Part A.

Part A consists of 3 periods: Screening Period, RCP, and OLE Period. Participants will be screened for eligibility for up to 6 weeks during the Screening Period. Approximately 36 eligible participants will be randomized in a 2:1 ratio to receive weight-based intravenous infusion of either ravulizumab or placebo during the double-blind RCP. Upon completing the last assessment of the RCP at Week 26, participants may continue into the OLE Period.

For each participant, the RCP ends, and the OLE Period begins at Week 26. During the OLE Period, participants in the ravulizumab group will continue to receive ravulizumab treatment, and participants in the placebo group will switch to receive ravulizumab treatment. Participants will receive ravulizumab while in the OLE Period until ravulizumab is either registered or approved (in accordance with country-specific regulations) or for up to 130 weeks (approximately 2.5 years), whichever occurs first.

Randomized Controlled Period

All participants randomized into the study are expected to complete the RCP and will be followed up until the end of the RCP.

Participants who discontinue study intervention will complete the RCP. Participants who require acute therapy with standard DM treatment therapy due to protocol-defined clinical worsening (CW) and complete all remaining visits of the RCP will be permitted to enter the OLE Period.

Participants who discontinue/withdraw from the study will not be permitted to enter the OLE Period. Participants who will not enter the OLE Period will not receive an infusion at Week 26.

OLE Period

Participants completing the OLE Period in Part A will have an End-of-Study Visit at Week 156 and a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention to collect information on concomitant medications, nonpharmacologic therapies and procedures, and AEs. Participants who discontinue study intervention will complete the visits and assessments of the OLE Period. Adjustments of "protocol allowed" DM medications will be permitted throughout the OLE Period. Participants who discontinue/withdraw from the study will complete an Early Termination Visit and a follow-up phone call.

An unblinded interim analysis for futility in Part A may be conducted when approximately 67% of participants have completed the Week 26 Visit or discontinued prematurely from the RCP of Part A. The unblinded interim analysis would be performed to assess futility by an Independent Data Monitoring Committee (IDMC). Details are provided in the IDMC Charter and the Interim Analysis Plan of Part A.

Participants from Part A of the study will not be enrolled in Part B (Phase 3) of the study, and therefore, will not contribute to the formal statistical hypothesis testing of Part B.

2. STATISTICAL HYPOTHESES

The null hypothesis associated with the primary endpoint is that there is no difference in TIS40 response rates between ravulizumab and placebo at Week 26 for Part A. The alternative hypothesis is that the response rates are different.

2.1. Multiplicity Adjustment

There will be no adjustment for multiplicity in Part A.

3. ANALYSIS SETS

The analysis sets for Part A are defined as follows:

Population	Description
Screened Set	All consented participants.
Enrolled Set	All consented participants excluding screen failures.
Safety Set (SS)	All participants who receive at least 1 dose of the study intervention. Participants will be analyzed according to the study intervention they actually received.
Randomized Set	All randomized participants grouped by randomized treatment group.
Pharmacokinetic Analysis Set (PKAS)	All participants who receive at least 1 dose of the study intervention and who have at least 1 postdose PK sample.
Pharmacodynamic Analysis Set (PDAS)	All participants who receive at least 1 dose of the study intervention and who have evaluable free or total complement component 5 data.
Immunogenicity Analysis Set	All participants who receive at least 1 dose of the study intervention and have at least 1 reportable ADA sample. Participants will be analyzed according to the study intervention they actually received.
OLE Set	All randomized participants who received at least 1 dose of ravulizumab starting from Week 26 onward.
All Ravulizumab-Treated Set	All participants who have received at least 1 dose of ravulizumab in the RCP and/or Open-Label Period.

4. STATISTICAL ANALYSES

4.1. General Considerations

All data collected in this study will be presented separately by treatment arm and period (RCP, OLE) using summary tables, figures, and data listings. All analyses will be performed using Statistical Analysis Software® (SAS®) version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

Summaries of study and participant characteristics (e.g., disposition, baseline characteristics and demographics, medical history, and protocol deviations, etc.) are described in Section 6.2.

All efficacy and safety analyses will be summarized for the RCP (up to Week 26) and the OLE Period. There may be additional summaries across the entire study period (RCP + OLE). The primary comparison will be ravulizumab treatment group versus the placebo treatment group during the RCP.

During the OLE Period, the participants who were randomized to placebo but later received ravulizumab will have additional variables created to reflect the data collected relative to the first dose of ravulizumab. At a minimum, all listings will include 2 sets of definitions for the following variables:

- Baseline value: Relative to the first randomized dose of placebo and relative to the first dose of ravulizumab in OLE.
- Study day: Relative to the first randomized dose of placebo and relative to the first dose of ravulizumab.
- Visit: Based on the actual study visit and visits re-aligned relative to the first dose of ravulizumab.

The descriptive analyses and presentations will be based on the types of variables being tested.

1. Overall summary of descriptive statistics for continuous variables will include but not limited to, number of observations, mean, standard deviation, median, minimum, and maximum, interquartile range, first quartile, and third quartile values. Minimum and maximum values will be reported to the same precision as the database.
2. Overall summary of descriptive statistics for categorical variables will include frequency counts and percentage of participants.

Formal statistical testing will be performed for the primary efficacy endpoint in the double-blind period. Testing will be conducted at the nominal 2-sided p-value of 0.20 level of significance.

Unless otherwise specified, data collected at any unscheduled visit and/or Early Termination will be included in by-participant listings, but not in the summary tabulations. However, unscheduled study visits will be used in the calculation of baseline values. Unscheduled visits/Early Termination visits will be included in the calculation of worst postbaseline values presented in shift tables.

4.1.1. Data Presentation for the 26-Week RCP

Data summaries for the 26-week RCP will be presented by randomized treatment groups (ie, ravulizumab and placebo).

4.1.2. Data Presentation for the OLE Treatment Period

Data summaries for the OLE Period will be presented by treatment sequence (ie, placebo to ravulizumab and ravulizumab to ravulizumab). For participants initially randomized to placebo, Baseline will be redefined as the last measurement taken prior to the first dose of ravulizumab in the OLE Period (eg, dose at Week 26).

4.1.3. Handling of Dropouts or Missing Data

No imputation will be performed for missing baseline values. For postbaseline data, any imputation will be specified in the derivation of the endpoint.

Missing outcome data due to the coronavirus disease 2019 (COVID-19) pandemic (eg, dropout due to COVID-19) is assumed missing-at-random.

Missing data for quality of life (QoL) instruments will be handled as specified in Section 6.3.

The following relevant IEs may occur during the study:

- Receipt of acute therapy with standard DM treatment therapy or prohibited medications
- Treatment discontinuation due to AE, lack of efficacy, or death

The handling of these relevant IEs is detailed in each analysis section.

4.2. Primary Analysis

The primary efficacy endpoint analysis will be based on the Randomized Set. Participants will be analyzed based on the randomized arm, regardless of the actual treatment received. The estimand for the primary analysis is defined in Table 2.

Table 2: Estimand for Primary Analysis

Estimand	Treatment	Population	Variable	Relevant Intercurrent Events	Population-Level Summary
Primary analysis	Ravulizumab Placebo	Randomization Set	TIS40 response rate at Week 26	• Receipt of acute therapy with standard DM treatment or prohibited medications • Treatment discontinuation due to an AE, lack of efficacy, or death during RCP	Difference in the percentage of TIS40 response between ravulizumab and placebo arms

Abbreviations: AE = adverse event; DM = dermatomyositis; RCP = Randomized Controlled Period; TIS40 =Total Improvement Score greater than or equal to 40.

4.2.1. Derivation of Endpoint

The primary endpoint is TIS40 response, defined as an International Myositis Assessment and Clinical Group - Total Improvement Score (IMACS-TIS) ≥ 40 at Week 26.

The International Myositis Assessment and Clinical Group (IMACS) developed a consensus on outcome measures and definitions of improvement that should be used in clinical studies for DM (Aggarwal, 2017). The consensus was reached for a joint analysis-based continuous model using absolute percentage change in 6 independent core set measures (CSMs; physician global activity, patient global activity, extramuscular disease activity, muscle strength, Health Assessment Questionnaire [HAQ], and muscle enzyme levels).

The improvement score within each CSM is calculated based on the absolute percentage change from Baseline (100 × [follow-up value - baseline value] / range) as shown Table 3. TIS ranges from 0 (worst improvement) to 100 (best improvement) is based on the improvement from Baseline and relative weight of each CSM; TIS will be calculated by summing the improvement scores from Baseline across the 6 CSMs at each Follow-up Visit.

Table 3: IMACS-TIS Algorithm

CSM (Range/Units)	Definition of "Improvement" Based on Absolute Percentage Change[a]	Level of Improvement Based on Absolute Percentage Change	Improvement Score
Physician global activity (0.0-10.0 cm)	"Improvement" is defined as a decrease, or negative percentage change, in the Physician Global Activity score	Worsening to 5% improvement	0
		> 5% to 15% improvement	7.5
		> 15% to 25% improvement	15
		> 25% to 40% improvement	17.5
		> 40% improvement	20
Patient global activity (0.0-10.0 cm)	"Improvement" is defined as a decrease, or negative percentage change, in the Participant Global Activity score	Worsening to 5% improvement	0
		> 5% to 15% improvement	2.5
		> 15% to 25% improvement	5
		> 25% to 40% improvement	7.5
		> 40% improvement	10
Manual muscle testing (MMT-8) (0-150)	"Improvement" is defined as an increase, or positive percentage change, in the MMT-8 score	Worsening to 2% improvement	0
		> 2% to 10% improvement	10
		> 10% to 20% improvement	20
		> 20% to 30% improvement	27.5
		> 30% improvement	32.5
HAQ (0-3)	"Improvement" is defined as a decrease, or negative percentage change, in the HAQ score	Worsening to 5% improvement	0
		> 5% to 15% improvement	5
		> 15% to 25% improvement	7.5
		> 25% to 40% improvement	7.5
		> 40% improvement	10
Enzyme[b,c] activity (enzyme specific[d])	"Improvement" is defined as a decrease, or negative percentage change, in the enzyme with the most abnormal activity level	Worsening to 5% improvement	0
		> 5% to 15% improvement	2.5
		> 15% to 25% improvement	5
		> 25% to 40% improvement	7.5
		> 40% improvement	7.5
Extramuscular disease activity (0.0-10.0 cm)	"Improvement" is defined as a decrease, or negative percentage change, in extramuscular disease activity score	Worsening to 5% improvement	0
		> 5% to 15% improvement	7.5
		> 15% to 25% improvement	12.5
		> 25% to 40% improvement	15
		> 40% Improvement	20

[a] Absolute percentage change is calculated as follows: $100 \times \left(\frac{\text{Follow-up value} - \text{baseline value}}{\text{Range}}\right)$.

[b] The muscle enzyme that has the most abnormal serum activity is defined as the enzyme with the highest Baseline level as a percentage of the ULN for the relevant enzyme.

[c] The most abnormal muscle enzyme will be selected from the following at Baseline and followed over time: creatine kinase; aldolase; alanine aminotransferase; aspartate aminotransferase; and lactate dehydrogenase.

[d] The range for each enzyme will be defined based on a multiple of the ULN for that enzyme as follows: creatinine kinase range = 15 × ULN; aldolase range = 6 × ULN; alanine aminotransferase, aspartate aminotransferase, and lactate ranges = 3 × ULN.

Abbreviation: CSM = core set measure; HAQ = Health Assessment Questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Group - Total Improvement Score; MMT = manual muscle testing; ULN = upper limit of normal

4.2.2. Main Analytical Approach

The primary endpoint measure will be assessed at Week 26 based on the TIS score detailed in Section 4.2.1.

Participants will be defined as a responder at Week 26 if:

1. The participant achieves TIS ≥ 40 at Week 26 and
2. The participant did not have a relevant IE up to and including Week 26 (defined in Section 4.2 and Table 2)

Otherwise, the participant will be counted as a non-responder at Week 26 in the randomized treatment arm.

The proportions of participants with a TIS ≥ 40 response at Week 26 in each treatment group with an exact 2-sided 80% CIs using the Clopper-Pearson method will be presented.

The differences in proportions between treatment arms, along with 2-sided 80% confidence intervals (CIs) using Chan and Zhang method (Chan, 1999), will be presented. Barnard's unconditional exact method will be applied to test whether there is a difference in the proportions between the 2 treatment groups.

The analysis as stated above will also be performed at earlier scheduled visits (Weeks 2, 10, and 18), but statistical testing will not be conducted at earlier timepoints. Additionally, a table summarizing the completeness of the TIS values at each scheduled visit will be presented. A listing of participants with an intercurrent event will be also generated.

Plots will be generated to display the proportion of responders (along with 80% exact CIs) by scheduled visit and treatment arm during the RCP.

4.2.3. Sensitivity Analyses

To assess the robustness of the primary endpoint due to the impact of missing data during the RCP, the following sensitivity analysis will be conducted.

The following imputation methods will be performed for missing TIS values in which a relevant IE did not occur up to and including the visit:

Imputation Method	Cases Where Imputation Method Used
Average of TIS values	• Missing TIS value at Week 10 or 18 where there are observed TIS values directly prior to and after the missed visit

Imputation Method	Cases Where Imputation Method Used
Treatment group mean	• Missing TIS value at Week 2 • Missing TIS values at all scheduled visits in the RCP
Last observation carried forward (LOCF)	• Missing TIS values at visits where no adjacent visits with no observed TIS values directly prior to and after the missed visit

Once the dataset is complete with no missing values of TIS, then TIS will be dichotomized and analyzed using the same manner as described in Section 4.2.2.

4.3. Secondary Endpoints

All secondary endpoints will be analyzed using the Randomized Set. There will be no formal testing of the secondary endpoints. Nominal p-values will be presented for endpoints where statistical testing is performed. Handling of the relevant IEs (acute therapy with standard DM treatment/prohibited medications and treatment discontinuation due to AE, lack of efficacy, or death) is described within each of the endpoints.

4.3.1. Total Improvement Score at Week 26

The Total Improvement Score (TIS) at Week 26 will be analyzed using an MMRM. Any data following the relevant IE will be set to missing, and the missing value will be imputed using the LOCF before the relevant IE.

The MMRM will include the observed TIS values at post-Baseline scheduled visits (Weeks 2, 10, 18, and 26) as the dependent variable. The model will include categorical effects of treatment, study visit, and treatment-by-study visit interaction. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. If the model using the unstructured correlation matrix fails to converge, then an alternative correlation structure resulting in the best model fit based on the Quasi-likelihood information criterion (QIC) (ie, smallest QIC) will be used among the following correlation structures: autoregressive (1), Toeplitz, and exchangeable.

At each visit, the least square (LS) mean with corresponding standard error and 80% CIs will be displayed by treatment arm. The LS mean treatment difference (ravulizumab - placebo) in TIS at Week 26 will be presented along with the 80% CI along with the corresponding p-value.

Descriptive statistics will also be generated by treatment arm at each scheduled visit.

LS means (± SEM) figure of TIS by treatment arm will be plotted.

4.3.2. Change From Baseline in Cutaneous Dermatomyositis Disease Area and Severity Index Activity Score at Week 26

The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) instrument measures activity and damage in the skin while the Clinician or Clinical-Investigator examines the participant. A summary score of Total activity and total damage are collected at each scheduled visit. Any data following the relevant IE will be set to missing, and the missing value will be imputed using the LOCF before the relevant IE.

Change from Baseline in in Total Activity Score at Week 26 will be analyzed using an MMRM. The MMRM model will include the observed Total Activity Score values at post-Baseline visits (Weeks 2, 10, 18, and 26) as the dependent variable. The model will include categorical effects of treatment, study visit, treatment-by-study visit interaction, and adjust for baseline Total Activity Score. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. If the model using the unstructured correlation matrix fails to converge, then an alternative correlation structure resulting in the best model fit based on the QIC (ie, smallest QIC) will be used among the following correlation structures: autoregressive (1), Toeplitz, and exchangeable.

At each visit, the LS mean with corresponding standard error and 80% CIs will be displayed by treatment arm. The LS mean treatment difference (ravulizumab - placebo) in the change from Baseline in Total Activity Score at Week 26 will be presented along with the 80% CI and corresponding p-value.

Descriptive statistics of actual values and change from Baseline in Total Activity Score will also be generated by treatment arm at each scheduled visit.

LS mean (± SEM) figures of change from Baseline in Total Activity Score by treatment arm will be plotted.

Summaries of Total Damage Score will be descriptive. actual values and change from Baseline in total damage score will be presented by treatment arm and scheduled visit.

4.3.3. Change From Baseline in 5 IMACS CSMs at Week 26

Change from Baseline in the 5 IMACS Core Set Measures (CSMs) at Week 26 will be analyzed using an MMRM. The 5 IMACS CSMs are comprised of (1) extramuscular disease activity, (2) physician global activity assessment, (3) patient global activity assessment, (4) manual muscle testing (MMT-8), and (5) HAQ. Any data following the relevant IE will be set to missing, and the missing value will be imputed using the LOCF before the relevant IE.

For each of the 5 CSMs, the outcome variable is change from Baseline in CSM at Weeks 2, 10, 18, and 26 and will include fixed effects of treatment arm (ravulizumab, placebo), visits (Weeks 2, 10, 18, and 26), treatment by visit interaction term, and adjustment for baseline of the core set measure. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. The Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. If the model using the unstructured correlation matrix fails to converge, then an alternative correlation structure resulting in best model fit based on the QIC criterion (ie, smallest QIC) will be used among the following correlation structures: autoregressive (1), Toeplitz, and exchangeable.

Within each CSM, the LS mean with corresponding standard error and 80% CIs will be displayed by treatment arm and visit. The LS mean treatment difference (ravulizumab - placebo) in the CSM at Week 26 will be presented along with the 80% CI along with the corresponding p-value.

In addition, change from Baseline in each of the muscle enzymes (sixth CSMs) will be analyzed using the MMRM model as specified above. A separate model for each muscle enzyme (creatine

kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase) will be generated.

Descriptive statistics of actual and change from Baseline in the 5 CSM will also be generated by treatment arm at each scheduled visit.

4.3.4. Response Related to Muscle Enzymes - Normalization of Most Abnormal Baseline Enzyme at Week 26

Muscle enzymes are classified as the following 5 laboratory parameters: creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase. For each participant, at Baseline, the most abnormal muscle enzyme is the laboratory parameter with the highest ratio (result/ULN) among the 5 laboratory parameters. Normalization of the most abnormal Baseline enzyme will be achieved if the result is less than the ULN (eg, ratio ≤ 1).

Participants will be defined as a responder at Week 26 if:

1. The participant achieves normalization of the most abnormal baseline muscle enzyme (eg, ratio ≤ 1) at Week 26 and
2. The participant did not have a relevant IE (defined in Section 4.2 and Table 2) up to and including Week 26 and
3. The participant did not have normal muscle enzymes at Baseline.

Otherwise, the participant will be counted as a non-responder in the randomized treatment arm.

The proportions of participants with a normalization of the most abnormal muscle enzyme at Week 26 in each treatment group, along with exact 2-sided 80% CIs using the Clopper-Pearson method, will be presented. The differences in proportions between treatment arms, along with 2-sided 80% CIs using the Chan and Zhang method (Chan, 1999), will be presented. Barnard's unconditional exact method will be applied to test whether there is a difference in the proportions between the 2 treatment groups.

The analysis as stated above will also be performed at earlier scheduled visits (Weeks 2, 10, and 18), but statistical testing will not be conducted.

4.3.5. CDASI Response (7-Point Improvement) at Week 26

A decrease from Baseline in CDASI Activity Score is considered an improvement.

Participants will be defined as a responder at Week 26 if:

1. The participant achieves a decrease from Baseline of at least 7 points or greater at Week 26 and
2. The participant did not have a relevant IE (defined in Section 4.2 and Table 2) up to and including Week 26

Otherwise, the participant will be counted as a non-responder in the randomized treatment arm.

The proportions of participants with a CDASI response of 7-point improvement or greater at Week 26 in each treatment group, along with exact 2-sided 80% CIs using the Clopper-Pearson method, will be presented. The differences in proportions between treatment arms, along with 2-sided 80% CIs using the Chan and Zhang method (Chan, 1999), will be presented. Barnard's

unconditional exact method will be applied to test whether there is a difference in the proportions between the 2 treatment groups.

The analysis as stated above will also be performed at earlier scheduled visits (Weeks 2, 10, and 18), but statistical testing will not be conducted.

Plots will be generated to display the proportion of responders (along with 80% CIs) by scheduled visit and treatment arm.

4.3.6. Cutaneous Dermatomyositis Activity Physician's Global Assessment Response (Almost Clear or Clear) at Week 26

The Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA) is a scale used to measure disease severity in participants with skin disease. It is a 5-point Likert scale (0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe) assigned by the Investigator to describe the overall appearance of lesions at a visit.

Participants will be defined as a responder at Week 26 if:

1. The participant response is almost clear or clear at Week 26 and
2. The participant did not have a relevant IE (defined in Section 4.2 and Table 2) up to and including Week 26 and
3. The participant demonstrated an improvement from Baseline (eg, mild at baseline to almost clear at Week 26 and almost clear at baseline to clear at Week 26).

Otherwise, the participant will be counted as a non-responder in the randomized treatment arm.

The proportions of participants with a CDA-IGA response (almost clear or clear) at Week 26 in each treatment group along with an exact 2-sided 80% CIs using the Clopper-Pearson method will be presented. The differences in proportions between treatment arms, along with 2-sided 80% CIs using Chan and Zhang method (Chan, 1999), will be presented. Barnard's unconditional exact method will be applied to test whether there is a difference in the proportions between the 2 treatment groups.

The analysis as stated above will also be performed at earlier scheduled visits (Weeks 2, 10, and 18), but statistical testing will not be conducted.

4.3.7. TIS20 Response at Week 26

A TIS20 response is defined as an IMACS-TIS $\geq$ 20.

Participants will be defined as a responder at Week 26 if:

1. The participant achieves TIS $\geq$ 20 at Week 26 and
2. The participant did not have a relevant IE up to and including Week 26 (defined in Section 4.2 and Table 2)

Otherwise, the participant will be counted as a nonresponder at Week 26 in the randomized treatment arm.

The analysis method as stated in Section 4.2.2 will be used to assess TIS20 at Week 26.

4.3.8. TIS60 Response at Week 26

A TIS60 response is defined as an IMACS-TIS ≥ 60.

Participants will be defined as a responder at Week 26 if:

1. The participant achieves TIS ≥ 60 at Week 26 and
2. The participant did not have a relevant IE up to and including Week 26 (defined in Section 4.2 and Table 2)

Otherwise, the participant will be counted as a nonresponder at Week 26 in the randomized treatment arm.

The analysis method as stated in Section 4.2.2 will be used to assess TIS60 at Week 26.

4.3.9. Time to First Response of TIS20, TIS40, and TIS60

Time to first response of TIS20, TIS40, and TIS60 is defined as the time between randomization date and the date of the first response (response as defined in Section 4.3.7, Section 4.2.2, and Section 4.3.8, respectively).

Participants without a TIS response will be censored as follows:

- If the participant had a relevant IE, then the censor date will be the last scheduled TIS assessment prior to the relevant IE.
- If the participant did not have a relevant IE, then the censor date will be the last scheduled TIS assessment. If there are no postbaseline TIS values, then the censor date will be the date of randomization.

Time to first response = date of response/censor date - randomization + 1

The distribution of time to response will be estimated using Kaplan-Meier method and compared between the treatment arms during the RCP. A log-rank test will be generated to test for differences in the distribution of time to first TIS response by arms. A Cox-proportional regression model with treatment intervention will be performed. The hazard ratio and corresponding 80% CIs and p-value will be presented.

Kaplan-Meier plots of time to first response of TIS20, TIS40, and TIS60 will also be generated.

4.3.10. CW During RCP at 2 Consecutive Visits

If a participant meets any of the following criteria on 2 consecutive visits during the RCP, then the participant will be defined as meeting the criteria for CW:

1. Physician's global activity visual analog scale (VAS) worsening ≥ 2 cm and manual muscle testing subset of 8 muscles (MMT-8) worsening ≥ 20% compared with Baseline
2. Global extramuscular disease activity worsening ≥ 2 cm on the Myositis Disease Activity Assessment Tool VAS compared to Baseline
3. Any 3 of 5 CSMs (excluding muscle enzymes) worsening by ≥ 30% compared with Baseline

The same criteria need not be met at both visits. A summary of the overall number of participants who met CW by treatment arm will be presented. A separate listing of the participants who met CW along with the criteria will be presented.

An additional analysis that will also include any participant who achieves CW during the RCP at a visit (for instance, including any participant who achieves CW at Week 26 and is unable to confirm the event during the RCP) will be performed.

4.3.11. Receipt of Acute Therapy With Standard DM Treatment

Acute therapy with standard DM treatment therapy may be provided during the RCP if the participant met CW or for other safety reasons. Any participants who receive acute therapy with standard DM treatment medication will need to discontinue study intervention. A summary of the overall number of participants who received acute therapy with standard DM treatment during the RCP will be summarized by treatment arm. A separate listing of the participants who receive acute therapy with standard DM treatment will be presented.

4.4. Exploratory Endpoints

All exploratory endpoints will be analyzed using the Randomized Set. These analyses will be descriptive in nature. For these endpoints, if any participant experiences a relevant IE of acute therapy with standard DM treatment/prohibited medication or treatment discontinuation due to AE, lack of efficacy, or death, the data will be set to missing after the IE and there will be no imputation.

4.4.1. Change From Baseline in EQ-5D-5L at Week 26

The European Quality of Life Health 5-item questionnaire dimensions 5-level (EQ-5D-5L) is self-assessed instrument. This instrument consists of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and VAS. The VAS ranges from 0 to 100, where lower values represent the worst QoL.

Descriptive statistics of actual and change from Baseline in VAS will be presented by treatment and scheduled visit. For each of the 5 domains, categorical summaries of the percentage of participants reporting ordinal responses (1 to 5) will be presented by treatment and scheduled visit. In addition, an overall shift table of Baseline to worst post-Baseline during the RCP will be generated by treatment arm for each of the 5 domains.

4.4.2. Change From Baseline in PROMIS-29 v2.1 Domains at Week 26

The Patient-Reported Outcomes Measurement Instrument System (PROMIS)-29 v2.1 is a QoL instrument used to assess pain intensity on a Likert scale for each of the health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using 4 items per domain. For each of the health domains, a total score will only be calculated if there are no missing items per domain. The total score will be the sum of the responses for each question.

Descriptive statistics of actual and change in total score will be presented by treatment arm and scheduled visit.

4.4.3. Change From Baseline in Short Form Health Survey (36 Questions Version) at Week 26

The Short Form Health Survey (36 Questions Version) (SF-36; Version 2.0) is a 36-item self-report of health-related QoL (HR-QoL). It contains 8 subscales measuring different domains of HR-QoL: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The 2 summary scores are the physical component summary (PCS) and the mental component summary (MCS). There is no single overall score for the SF-36.

Descriptive statistics of actual and change in each of the 8 subscales, as well as the PCS score and MCS score, from Baseline will be generated by treatment arm and scheduled visits.

4.4.4. Change in DM Symptoms Captured in DM-DSQ at Week 26

Analyses of this endpoint will be summarized in a separate SAP.

4.4.5. Change From Baseline in Participant Self-Assessment of Disease Activity at Week 26

Analyses of this endpoint will be summarized in a separate SAP.

4.4.6. Exploratory Biomarkers

Exploratory biomarker analyses will be outlined in a separate SAP.

4.4.7. Change from Baseline Using Scale to Measure Pruritus (5D-Itch Scale) at Week 26

Descriptive statistics of actual and change from Baseline in total 5D score at each visit will be generated.

4.4.8. Incidence of Protocol-Defined CW During RCP

A time-at-risk-adjusted incidence rate will be calculated. This incidence rate is defined as the number of participants who experience CW divided by the total person-years at risk for the event. CW during the RCP will be defined as a participant meeting the criteria as specified in Section 4.3.10 at 2 consecutive visits. The total person-years at risk will be defined differently for participants with and without the event of CW. For participants with an event, the risk is defined as (date of the criteria being met for CW - first dose date + 1)/365.25. If the participant did not experience an event, the risk is defined as (latest visit date of TIS during the RCP - first dose date + 1)/365.25. Total person-years at risk will be the sum of the person-years at risk for all participants in each treatment group. A summary table displaying the total person-years at risk and the number of participants with an event will be displayed.

4.4.9. Change From Baseline in Handheld Dynamometry Performance at Week 26

Handheld dynamometry is a procedure for quantitative strength testing. Muscle strength testing will be performed at baseline and Week 26. Derivations are specified in Section 6.1.6.

Descriptive statistics of actual values and change from Baseline will be summarized by visit for the handheld dynamometry (HHD) data.

4.4.10. Change From Baseline in 30-second Chair Stand Test (30s CST) at Week 26

The 30-second Chair Stand Test (30s CST) will count the number of times the participant is able to stand in 30 seconds at baseline and Week 26. Descriptive statistics will be generated.

4.4.11. Change From Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale at Week 26

Descriptive statistics of actual and change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) scores at each visit will be generated.

4.5. OLE Analysis

Descriptive analyses of key safety and efficacy will be generated based on data collected as of the data cutoff in the OLE Set.

The efficacy analyses may include endpoints such as, but not limited to, the following:

- TIS over time
- TIS response rate for TIS20, TIS40, and TIS60
- Change from Baseline in CDASI

A subset of key safety tables in the OLE Set such as, but not limited to, disposition, baseline disease characteristics, total exposure and adverse events (AEs) may also be summarized. For efficacy and safety summaries of the OLE population, the Baseline will be relative to the first dose of study intervention.

Additionally, similar analyses as noted above may also be conducted using the All Ravulizumab-Treated Set summarizing data across the study periods (RCP and OLE). For these summaries, the Baseline will be relative to the first dose of ravulizumab.

4.6. Safety Analyses

The safety and tolerability of ravulizumab will be assessed based on Exposure, Adverse Events, clinical laboratory findings, vital signs findings, electrocardiogram (ECG) abnormalities, and physical examinations. All safety analyses will be performed on the Safety Set (SS) based on the actual treatment received.

4.6.1. Exposure

Summaries of exposure during the RCP will include the following categories such as, but not limited to, total number of infusions received per participant, total dose (mg), cumulative dose drug exposure, number of missed infusions, and number of interrupted infusions.

Treatment duration will be calculated (in weeks) as the difference between the last dose date and the first dose date + 1 divided by 7. This will be summarized as descriptive statistics.

In addition, the total number of participants who missed an infusion and reason will be summarized by treatment group and overall. A by-participant listing of participants with a missed infusion will be generated separately with reason for not done.

4.6.2. Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA Version 26.0 or later) and displayed in tables using System Organ Class (SOC) and Preferred Terms (PT). Treatment-emergent AEs are defined as any AE with a start date on or after the first dose of study intervention in the RCP.

An AE overview table will be tabulated. This table will include the number and percentage of participant in the following categories such as, but not limited to, the following:

- At least 1 treatment-emergent adverse event (TEAE)
- At least 1 drug-related TEAE
- At least 1 TEAE of Grade 3, 4, or 5
- At least 1 serious TEAE
- At least 1 serious related TEAE
- At least 1 adverse event of special interest (AESI)
- At least 1 AE leading to treatment discontinuation
- At least 1 drug-related AE leading to treatment discontinuation
- At least 1 infusion-related reaction

Tabulations by SOC and PT displaying the number of participants (percentage) and total event will be generated for the following tables:

- All TEAEs
- TEAEs of Grade 3, 4, or 5
- AEs related to treatment
- AEs related to treatment by maximum severity
- AESI
- Serious Adverse Events (SAEs)
- SAEs related to treatment
- AEs leading to treatment discontinuation
- Infusion Associated Related Reactions

Separate listings will be provided for deaths, SAEs, and any AEs leading to study withdrawal or treatment discontinuation. In addition, a separate AE listing will be generated for any AE related to COVID-19.

In addition, there will be a separate listing for any pretreatment AEs. These AEs will not be included in the summary tables of TEAEs. Pretreatment AEs are defined as AEs that start after informed consent but before the first dose of study intervention.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Parameters

Laboratory assessments are defined in the Protocol Section 10.3.

Clinical safety laboratory parameters will be expressed in standard international units. Laboratory data collected and recorded below lower limit of quantification (LLOQ) will be set to LLOQ for calculation of summary statistics (eg, < 400 U/L will be imputed as 400). Summaries will only include data analyzed from a central laboratory.

Summaries for each laboratory parameter (hematology, chemistry, coagulation, and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics at each scheduled visit. Descriptive statistics include actual value and change from Baseline at each scheduled visit.

Shift tables will be generated to summarize shifts from baseline categories to the worst postbaseline categories with directionality specified for any laboratory values, which could be reported in either direction (eg, above ULN or below ULN). Clinical laboratory tests with normal ranges will be classified as low, normal, and high. For these tests, abnormal values will be flagged in the listings with H when the value is higher than the upper limit of the reference ranges and with L when the value is lower than the lower limit of the reference ranges.

For hematology and chemistry laboratory values, summary tables of potentially clinically significant abnormalities will also be provided.

Separate listings of laboratory data collected from central compared and local laboratories will be generated. Out-of-range laboratory results will be identified in listings.

Boxplots will be presented over time by scheduled visit for planned chemistry and hematology parameters.

4.6.3.2. Vital Signs

Vital signs include systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]), and oxygen saturation (%).

Tabular summaries of actual and change from Baseline in each vital sign will be summarized at each scheduled visit.

A by-participant listing of vital signs will be also presented.

4.6.3.3. Electrocardiograms

ECG parameters include heart rate, PR interval, QRS interval, RR interval, QT interval, QT interval corrected using Fridericia's formula (QTcF), and interpretation.

For ECG parameters, these will be summarized using descriptive statistics of the actual values and change from Baseline by scheduled visit. In addition, the number and percentage of participants with normal, abnormal and not clinically significant, and abnormal and clinically significant will be summarized.

Shift tables from baseline to postbaseline maximum QTcF and maximum change from Baseline in QTcF will be summarized. The incidence of notable ECG changes from Baseline in maximum absolute intervals (≤ 450 ms, > 450 to ≤ 480 ms, > 480 to ≤ 500 ms, and > 500 ms), as well as in QTcF, maximum changes from Baseline (≤ 30 ms, > 30 to 60 ms, and > 60 ms) over all post-treatment evaluations will be summarized.

A by-participant listing of ECG data will also be provided.

4.6.3.4. Physical Examinations

During the study, full and abbreviated physical examinations will be conducted throughout the study. Adverse changes from Baseline in physical examinations will be classified as AEs and analyzed accordingly. Categories of physical examinations results will be summarized by treatment group.

4.7. Other Analyses

This study will also include analyses of PK/PD and immunogenicity of ravulizumab as described in each section.

4.7.1. PK/PD Analyses

The PKAS and PDAS will be used for PK/PD analyses. PK concentrations recorded below LLOQ will be set to LLOQ for calculation.

Individual serum concentrations of ravulizumab will be presented in data listings and summarized separately using descriptive statistics such as (N, n, arithmetic mean, SD, CV%, median, minimum, and maximum) by sampling timepoint. Graphics of mean serum concentration-time profiles will be constructed. Graphics of serum concentration-time profiles for individual participants may also be provided.

PD analyses will be performed using the PDAS. Descriptive statistics will be presented by summarizing absolute values, changes from Baseline, and percentage changes from Baseline in free and total C5 serum concentrations over time, as appropriate. Boxplots of absolute values of free and total free C5 serum concentrations by study visit will be constructed.

Assessments of ravulizumab PK/PD relationship may be explored using data from this study or in combination with data from other studies.

4.7.1.1. Immunogenicity Analyses

All immunogenicity analyses will be performed on the Immunogenicity Analysis Set.

Immunogenicity variables include antidrug antibody (ADA) status, ADA response category, and ADA or neutralizing antibody (NAb) incidence and titer over the duration of the study as follows.

The summaries of ADA incidence over the duration of the study will include the following response categories:

- **ADA negative:** An ADA-negative signal in the ADA assay at all timepoints collected for ADA analysis

- **ADA positive:** An ADA-positive signal in the ADA assay at any timepoint collected for ADA analysis

Participants who are ADA positive may be further categorized into ADA response categories as follows:

- **Pre-existing immunoreactivity:** An ADA-positive response with either of the following 2 conditions met:
  - ADA-positive response at Baseline with all post-first dose ADA results negative

  OR

  - ADA-positive response at Baseline with all post-first dose ADA responses < 4-fold over the baseline titer level
- **Treatment-emergent ADA responses:** An ADA-positive response post-first dose when baseline results are negative or missing
- **Treatment-boosted ADA responses:** An ADA-positive response post-first dose that is ≥ 4-fold over the baseline titer level when the baseline result is positive

Study participants with a treatment-emergent or treatment-boosted ADA responses may be further categorized as follows:

- **Persistent**: ADA responses with 2 or more consecutive ADA-positive samples separated by at least a 16-week period, with no ADA-negative samples in between, irrespective of missing samples
- **Indeterminate:** ADA-positive samples only at the last collected sample
- **Transient:** An ADA response that is neither a persistent nor an indeterminate response

ADA-positive samples will be further characterized for neutralizing activity in the NAb assay. NAb status categories are as follows:

- NAb positive
- NAb negative

Association of immunogenicity with impact on exposure, safety, and efficacy:

- Association of immunogenicity with an impact on exposure: Associations between ADA response categories or NAb and systemic exposure to ravulizumab may be explored to assess the potential impact of immunogenicity on drug concentration-time (PK) profiles.
- Association of immunogenicity with an impact on safety: Associations between ADA response categories or NAb and serious and severe AEs may be explored, including SAEs such as systemic hypersensitivity, anaphylaxis, injection/infusion site reactions lasting > 24 hours, and other immune-related SAEs.

- Association of immunogenicity with an impact on efficacy: Associations between ADA response categories or NAb and key efficacy endpoints or variables may be explored to assess the impact of immunogenicity on drug efficacy.

4.8. Subgroup Analyses

No subgroup analyses will be performed.

4.9. Interim Analyses

An unblinded interim analysis may be conducted for futility when approximately 24 (67%) of all participants complete the Week 26 Visit or have discontinued prematurely. The comparative primary and safety data will be assessed at this interim analysis. There is no plan to alter Part A study design, and thus, no adjustment is needed for Type 1 error at the final analyses.

The unblinded interim analysis will be conducted by the IDMC. The IDMC SAP includes details of the interim analysis.

At the time of the interim analysis, there will also be additional analyses generated to support an Unblinded Review Committee (independent of the study team). The details of the Unblinded Review Committee are specified in a Unblinded Review Committee Charter document.

4.10. Changes to Protocol-Planned Analyses

Not applicable.

5. SAMPLE SIZE DETERMINATION

A total number of 36 participants will be randomized into the study with a 2:1 (ravulizumab:placebo) allocation ratio to ensure approximately 80% power to detect a difference (ravulizumab−placebo) of 45% in TIS40 response rates with a 2-sided Type 1 error of 0.2, assuming a placebo response rate of 23% and an approximately 20% dropout rate.

The sample size was calculated in PASS2022 using the 2-sample test for the difference of proportions with a pooled estimate of variance for the primary endpoint (TIS40).

6. SUPPORTING DOCUMENTATION

6.1. Technical Specifications for Derived Variables

6.1.1. Baseline Definitions

Baseline Definitions Applied to the RCP:

To calculate TIS, a Baseline must be defined for each of the 6 CSMs.

For 5 of the CSMs (excluding muscle enzymes), the Baseline of the CSM will be defined as the latest non-missing value prior to the first dose of study intervention (ravulizumab or placebo).

For the sixth CSMs (muscles enzymes, which consist of creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase), the latest non-missing value prior to the first dose of study intervention will be selected. The Baseline of the most abnormal muscle enzyme will be the laboratory value of the enzyme with the highest ratio (result/ULN).

For other parameters, the Baseline will be defined as the latest nonmissing value prior to the first dose of study intervention (ravulizumab or placebo), unless otherwise specified.

For the placebo participants who later receive ravulizumab during the OLE Period, an additional Baseline will be summarized. The Baseline will be defined as above, but it will be relative to the first dose of ravulizumab.

6.1.2. Visit Windows

For tables and figures, all summaries by timepoint during the RCP will be tabulated and analyzed per the scheduled visit as recorded on the electronic case reports forms (eCRF) even if the assessment is out of window. For shift table summaries, these will include unscheduled visits.

Unless otherwise specified, data collected at an unscheduled visit or Early Termination will be included in by-participant listing and/or spaghetti plots figures, but no assignment of the scheduled visit will be made for the purposes of tabulations. For the calculation of baseline, unscheduled visit will be considered. For shift tables, unscheduled visits or Early Terminations visits will be considered for worst post-baseline.

For the placebo participants who later receive ravulizumab during the OLE Period, an additional visit will be summarized. The Baseline will be remapped relative to ravulizumab (eg, Week 26 remapped to Day 1, and Week 28 relative to Week 2).

6.1.3. Study Day

Study Day 1 will be the defined as the first date of study intervention (ravulizumab or placebo). Day is relative to the first dose date of the study intervention for all participants.

If the assessment is after the first dose date, the study day will be calculated as follows:

- Study day = date of assessment - date of the first dose of study intervention + 1

If the assessment is before the first dose date, the study day will be calculated as follows:

- Study day = date of assessment - date of the first dose of study intervention

For participants who were randomized to placebo but later received ravulizumab, the participant will have additional variables in listings. These variables will reflect the data closest to the first dose of ravulizumab.

- Baseline value: relative to the first dose of placebo and relative to the first dose of ravulizumab in OLE
- Study day: relative to the first randomized dose of placebo and relative to the first dose of ravulizumab
- Visit: based on actual study visit and visits remapped relative to the first dose of ravulizumab

6.1.4. Derivation of TEAEs for Incomplete or Missing Date of Onset

If both start and end dates of AEs are completely missing, no imputation will be performed and those AEs will be considered treatment emergent.

If the start date is partial:

1. If only the day is missing:
    a. If the month/year of the start date is the same as those of the first study intervention administration date, then the missing day will be imputed as the smaller nonmissing value of (day of the first study intervention administration, day of the AE end date).
    b. Otherwise, impute the missing day as "01."
2. If both day and month are missing:
    a. If the year of the AE start date coincides with the year of the first study intervention administration date, the partial start date will be set as the first study intervention date. If this leads to a date after the AE end date, then the missing day and month of the AE start date will be imputed as the day and month of the AE end date.
    b. If the year of the AE start date is different from the year of the first study intervention administration date, the missing day and month of the AE start date will be imputed as "01" and "01."

If the stop date is partial:

1. If only the day is missing:
    a. The missing day will be imputed as the last of the month, adjusting for the leap year.
2. If both day and month are missing:
    a. If the year of the AE end date coincides with the maximum of (the year of the first study intervention administration date or the year of the last study intervention administration), then the missing month will be imputed as the month of the corresponding study intervention administration date (first or last) and the missing day will be imputed as the last of the month adjusting for the leap year.
    b. Otherwise, the missing day and month of the AE stop date will be imputed as the "31" and "12."

6.1.5. Derivation of Prior or Concomitant Medications for Missing or Incomplete Dates

If both start and end dates of medications are completely missing, no imputation will be performed, and those medications will be considered both prior and concomitant medications.

If the end date is partial:

1. If only the day is missing
    a. If the year and month coincide with those of the last study intervention administration date, then the end of medication will be set to the last study intervention administration date.
    b. If the year and month do not coincide with those of the last study intervention administration date, then the missing day will be imputed as the last day of the month considering leap year and month.
2. If both day and month are missing
    a. If the year coincides with that of the last study intervention administration date, then the missing month and day will be imputed as the month and day of the last study intervention administration.
    b. If the year does not coincide with that of the last study intervention administration date, then the missing month and day will be imputed as "12" and "31," respectively.

If the start date is partial:

1. If only the day is missing
    a. If the year coincides with that of the first study intervention administration date, then do the following:
    b. If the month does not coincide with that of the first study intervention administration date, then impute the missing day as "01."
    c. If the month coincides with that of the first study intervention administration date
        i. If the end date is greater than the first study intervention administration date, then impute the missing day as the day of the first study intervention administration date.
        ii. If the end date is less than or equal to the first study intervention administration date, then impute the missing day as the day of the end date of medication.
    d. If the year and the month do not coincide with those of the first dose date, then impute the missing day as "01."
2. If both day and month are missing:
    a. If the year does not coincide with that of the first study intervention administration date, then impute the missing month as "01" and missing day as "01."
    b. If the year coincides with that of the first study intervention administration date
        i. If the end date is greater than the first study intervention administration date, then impute the missing day and month as those of the first study intervention administration.

c. If the start date is completely missing, the missing start date will be set as the earlier of the first study intervention administration date and the end of the medication date.

For meningococcal vaccination, the missing end date will not be imputed.

6.1.6. Handheld Dynamometry

The HHD will be derived as follows:

- For each muscle, calculate the percent of Baseline: 100 × (Post-baseline raw value/Baseline raw value). If both the post-baseline and baseline values are 0, then the ratio=100. If the post-baseline value is greater than 0 but the baseline was zero, then the ratio is set to missing.
- Three Megascores will be summarized based on muscle location (upper limbs, lower limbs and total). The score for each will be derived as the average of the non-missing ratio for the muscles used in the calculation.
- Megascore is set to 100 at Baseline when HHD assessment is available.

6.2. Study and Participant Characteristics

6.2.1. Participant Disposition

A summary of participants who did not satisfy the inclusion/exclusion criteria will be presented. A summary of the participants will be tabulated for the following categories: Screen Failure, Randomized, Treated and each of the populations sets.

In addition, the number and percentage of participants who discontinued treatment, withdrew from study, and primary reasons for either discontinuation of treatment and/or withdrawal from study will be presented. Additionally, the number of participants who completed the RCP at the Week 26 Visit will also be displayed. A participant is defined as having completed the RCP at the Week 26 Visit if the participant has an assessment at that visit. The number and percentage of participants enrolled by site will be summarized by randomized arm and overall.

Data listings of those participants who withdrew and/or discontinued treatment including the associated reasons will also be presented. A separate listing of screening failure participants with the associated reason for screen failures will be generated. In addition, a listing will be generated for any modified visits that occurred on study with the reason for the modification (eg, COVID-19, travel, and participant refusal).

6.2.2. Baseline Characteristics and Demographics

All summaries for baseline characteristics and demographics will be based on the Randomized Set.

Descriptive statistics of demographic characteristics, including, but not limited to, age (years), age category (≥ 18 to < 65 and ≥ 65 years), sex, race, ethnicity, region, height, weight, and weight categories (≤ 30 to < 40 kg, ≥ 40 to < 60 kg, ≥ 60 kg to < 100 kg, and ≥ 100 kg), and body mass index will also be presented.

Additional disease characteristics will also be summarized. The disease characteristics include baseline values for 5 of the CSMs (ie, physician global activity assessment, participant global activity assessment, extramuscular disease activity, MMT-8, and HAQ), baseline CDASI Total Activity Score, baseline CDASI damage score, and baseline CDA-IGA category.

In addition, a summary of disease characteristics will be summarized. These characteristics include summaries, but are not limited to, age of diagnosis, duration of the DM diagnosis and current/prior DM medications (as reported on DM history page) and symptoms of the DM at Screening (eg, rash, calcinosis, and fatigue) and location of the joint swelling (eg, elbow, hip, and wrist).

By-participant listings of these baseline characteristics data will be presented.

6.2.3. Medical History

A complete medical history will be collected during Screening. The medical and surgical history will be coded using MedDRA (Version 25.0 or higher). Medical will be summarized for the SS by SOC, High Level Term, and PT. By-participant listings of medical history data will also be presented.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (Sep 2023 or later).

Prior medications are defined as medications that were taken prior to and stopped before the first dose of treatment (ravulizumab or placebo). Concomitant medications are defined as medications that were taken prior to and were ongoing while on study intervention or medication(s) taken on or after the first dose date of the study intervention. A tabular summary of the number and percentage of participants taking concomitant medications will be by anatomic therapeutic class (ATC) and PT. Data will be presented for the SS. A separate tabular summary of prior DM and concomitant DM medication use will be by ATC and PT.

Data listings for prior medications/concomitant medications by participant will be generated, and a separate listing for prior DM and concomitant DM medications will also be generated. There may also be additional summaries of steroid medications presented by ATC and PT.

6.2.5. Nonpharmacologic Therapies and Procedures, Hospitalizations, and Outpatient Medical Encounters

Separate listings will be generated for nonpharmacologic therapies and procedures, hospitalizations, and outpatient medical encounters.

6.2.6. Protocol Deviations

The number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants. Protocol deviations will be presented overall as well as separately for those related to COVID-19.

6.3. Instrument Scoring Details

6.3.1. Short Form Health Survey (36 Questions Version)

The SF-36 version 2 is a set of generic, coherent, and easily administered QoL measures. It has 36 items grouped in 8 dimensions measuring each of the following 8 health domains: physical functioning, social functioning, role limitations due to physical health, bodily pain, general health, mental health, role limitations due to emotional problems, and vitality. Eight health domains scores and 2 component scores (PCS, MCS) will be calculated. The OPTUM ProCoRE 1.5 Smart Measurement System will be used to derive the 8 domain scores and 2 component scores. The algorithms used by the software are described below (as excerpted from the User's Guide).

6.3.1.1. Data Cleaning and Item Recording

First, the data are checked for out-of-range values. Out-of-range values are any values that are outside the range of acceptable item response values for the SF-36 version 2 Health Survey. Out-of-range values will be converted to missing values. Next, 10 items (BP01, BP02, GH01, GH03, GH05, VT01, VT02, SF01, MH03, MH05) are reverse scored. Reverse scoring of these items is required so that higher item response values indicate better health for all SF-36 version 2.0 Health Survey items and summary measures.

6.3.1.2. Item Recalibration

For most of the SF-36 version 2 Health Survey items, research to date offers good support for the assumption of a linear relationship between the item scores and the underlying health concept defined by their scales. However, empirical work has shown that 2 items, GH01 and BP01, require recalibration to satisfy this important scaling assumptions. The bodily pain scale requires additional scoring rules because the items offer both different numbers and different content of response choices and administrations of Item BP02 depended on the response to an Item BP01 in past studies.

6.3.1.3. Computation of Raw Scale Scores

After recoding and recalibrating the required item values, a raw score is computed for each scale. This score is the simple algebraic sum of the final values for all items in that scale.

6.3.1.4. Transformation of Raw Scale Scores to 0 to 100 Scores

The next step involves transforming each raw scale score to a 0 to 100 scale. This transformation converts the lowest and highest possible scores to 0 and 100, respectively. Scores between these values represent the percentage of the total possible scores achieved.

6.3.1.5. Transformation of Raw Scale Scores to 0 to 100 Scores

The first step in T-score based scoring consists of standardizing each SF-36 version 2 Health Survey scale using a z-score transformation. A z-score indicates how far a score deviates from the mean in standard deviation units. The z-score for each scale is computed by subtracting the mean 0 to 100 score observed in the 2009 general US population from each SF-36 version 2 Health Survey scale score (0 to 100) scale and dividing the difference by the corresponding scale

standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent on the recall period option chosen by the user, based on the SF-36 version 2 Health Survey form used to collect the data being scored.

The next step of the T-score based scoring is to linearly transform each SF-36 version 2 Health Survey z-score to have a mean score of 50 and a standard deviation of 10. This is done by multiplying each SF-36 version 2 Health Survey z-score by 10 and adding the resulting product to 50. These are referred to as "norm-based" scores. The norm-based scores will be used for the 8 domain scores.

6.3.1.6. Scoring the SF-36 Version 2 Healthy Survey Component Summary Measure

The first step in scoring the component summary measures consists of standardizing each SF-36 version 2 Health Survey scale using a z-score transformation. The z-score for each scale is computed by subtracting the mean 0 to 100 score observed in the 2009 general US population from each SF-36 version 2 Health Survey scale score (0 to 100) scale and dividing the difference by the corresponding scale standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent on the recall period option chosen by the user based on the SF-36 version 2 Health Survey form used to collect the data being scored.

After a z-score has been computed for each SF-36 version 2 Health Survey scale, the second step involves computation of aggregate scores for the physical and mental summaries using weights (factor score coefficients) derived from the 1990 general US population. These are the same weights as those used to score PCS and MCS from the SF-36 version 2 Health Survey. An aggregate physical score is computed by multiplying the z-score of each SF-36 version 2 Health Survey scale by its associated physical factor score coefficient and summing the 8 products. If any of the scale scores are missing, then the aggregate physical score is not computed. An aggregate mental score is computed by multiplying the z-score of each SF-36 version 2 Health Survey scale by its associated mental factor score coefficient and summing the 8 products. If any of the scale scores are missing, then the aggregate mental score is not computed.

The third step involves transforming the aggregate physical and mental summary scores to the T-score based (50, 10) scoring. This is done by multiplying each aggregate summary score obtained from the second step by 10 and adding the resulting product to 50.

6.3.1.7. Handling of Missing Items

The maximum data recovery option will be used for missing data estimation. This results in the application of algorithms that compute a scale score for those respondents who have answered at least 1 item that represents that construct. For the physical functioning scale, item parameters obtained through item response theory methods are used to estimate a missing value on an item based on a respondent's responses to answered items. For the 7 remaining scales, a person-specific estimate based on the mean response to the answered items on the scale is used to estimate a missing value. Additionally, a PCS and MCS score is calculated for those respondents who have calculated scores on at least 7 of the 8 SF-36 version 2 Health Survey scales. However, PCS is not estimated if the physical functioning scale is missing, and MCS is not estimated if the Mental Health scale is missing.

6.3.2. FACIT-Fatigue

The FACIT-Fatigue questionnaire consists of 13 items scored on a 5-point Likert scale (0 = not at all, 4 = very much). The FACIT-Fatigue subscale scoring guideline (version 4) will be used as follows (https://www.facit.org/measures/FACIT-Fatigue):

- All negatively stated items (ie, all items except An5 and An7 from the eCRF) are to be reversed by subtracting the response from 4.
- After reversing the proper items, all items are summed to obtain a score.
- The Fatigue subscale score is then calculated by multiplying the sum of the item by 13, then dividing by the number of items answered.

When there are missing data, prorating by subscale in this way is acceptable if more than 50% of the items were answered. The score has a range of 0 to 52, with higher scores indicating better QoL.

6.3.3. 5D-Itch Scale

The 5D-itch scale assesses the 5 domains of degree, duration, direction, disability, and distribution of pruritus. Participants rate their symptoms over the preceding 2-week period. The scores of each of the 5 domains are achieved separately and then summed together to obtain a total 5D score resulting in a range of scores from 5 to 25 (no to most severe pruritus). If any one item is missing the total score will be missing. The single-item domains (duration, degree, and direction) are captured on a Likert scale. The score for these domains is equal to the value recorded for the domain (ie, 1 to 5). The disability domain includes 4 items that assess the impact of itching on sleep, leisure/social activities, housework/errands, and work/school. The score for the disability domain is achieved by taking the highest score on any of the 4 items. For the distribution domain, the number of affected body parts is given a point total (0–2 = 1, 3–5 = 2, 6–10 = 3, 11–13 = 4, 14–16 = 5).

6.3.4. PROMIS-29

The PROMIS-29 version 2.1 tool is a 1 is a QoL instrument used to assess pain intensity on a 0 to 10 scale and 7 health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using 4 items per domain. For each of the health domains, a total score will only be calculated if there are no missing items per domain. The total score will be the sum of the responses for each question. The algorithms are described below in Section 6.3.4.1 (excerpted from the Scoring Manual).

6.3.4.1. Computation of Total Raw Scores

Each question usually has 5 response options ranging from 1 to 5. To find the total score for a short form with all questioned answered, sum the values of each response to the question. For example, for an 8-item form, the lowest possible score is 8 and the highest possible score is 40.

6.4. Additional Details on Statistical Methods

Below is an example of the SAS code to generate the primary endpoint model:

```
proc freq data = DATASET;
   by Visit;
   tables ARM * TIS40 / alpha=0.20 riskdiff;
   exact barnard riskdiff;
run;
```

6.5. Potentially Clinically Significant Criteria

Parameter	**PCSA Low**	**PCSA High**
Chemistry		
Potassium	< 3 mmol/L	≥ 6 mmol/L
Calcium	< 1.75 mmol/L	> 3.4 mmol/L
Sodium	≤ 129 mmol/L	≥ 155 mEq/L
Blood urea nitrogen		> 40 mg/dL
Creatinine		> 186 umol/L
Total bilirubin		> 2 × ULN
Alkaline phosphatase		> 3 × ULN
AST		> 3 × ULN
ALT		> 3 × ULN
Albumin	≤ 30 g/L	
Chloride	< 80 mmol/L	> 130 mmol/L
Glucose	< 3 mmol/L	
Hematology		
Hemoglobin	≤ 115 g/L (male) ≤ 95 g/L (female)	≥ 185 g/L (male) ≥ 165 g/L (female)
Platelets	< 100 10^9/L	> 800 10^9/L

7. REFERENCES

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ALXN1210-DM-310_SAP_PARTA_RCP_CDRC

Final Audit Report 2023-08-23

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By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAyWb0oK2FyUqv6D4Id5Nz-pQYzpEkwCux

"ALXN1210-DM-310_SAP_PARTA_RCP_CDRC" History

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Challenge: The user opened the agreement.
2023-08-22 - 6:38:34 PM EDT

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Challenge: The user opened the agreement.
2023-08-22 - 6:40:01 PM EDT

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