Janssen Pharmaceutical K.K. *

Statistical Analysis Plan

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Ustekinumab in Participants With Active Polymyositis and Dermatomyositis Who Have Not Adequately Responded to One or More Standard-of-care Treatments

Protocol CNTO1275DMY3001; Phase 3

STELARA® (ustekinumab)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K. in Japan.

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AMENDMENT HISTORY

Not Applicable.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AZA	azathioprine
BQL	below the lowest quantifiable sample concentration of the assay
CK	creatine kinase
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBL	database lock
DLCO	diffusing capacity of the lungs for carbon monoxide
DM	dermatomyositis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report forms
EDTA	ethylenediaminetetraacetic acid
FI-2	Functional Index-2
FVC	forced vital capacity
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HRCT	high-resolution computer tomography
ICF	informed consent form
ILD	interstitial lung disease
IMACS TIS	International Myositis Assessment and Clinical Studies Total Improvement Score
IQ	interquartile
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
MDAAT	Myositis Disease Activity Assessment Tool
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
MITAX	Myositis Intention to Treat Activity Index
MMF	mycophenolate mofetil
MMRM	mixed-effect model repeated measure
MMT	Manual Muscle Testing
MTX	methotrexate
MVV	maximal voluntary ventilation
NCI	National Cancer Institute
PD	pharmacodynamic
PFT	pulmonary function test
PK	pharmacokinetic
PM	polymyositis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	36-item short form
TAC	tacrolimus
TB	tuberculosis
VAS	Visual Analogue Scale
VC	vital capacity
WBC	white blood cell

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacokinetics/pharmacodynamic (PK/PD) and response biomarkers of ustekinumab treatment. This document provides analysis plan for all four DBLs of CNTO1275DMY3001 study, which will occur at Week 24, Week 52 Week 72 and Week 88.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate the efficacy of ustekinumab in participants with active polymyositis and dermatomyositis (PM/DM) despite receiving 1 or more standard-of-care treatments (eg, glucocorticoids and/or immunomodulators).

Secondary Objectives

The secondary objectives are to evaluate the following in participants with active PM/DM despite receiving 1 or more standard-of-care treatments (eg, glucocorticoids and/or immunomodulators):

- Improvement in organ-specific (musculoskeletal, mucocutaneous, etc) measures of PM/DM disease activity
- Reduction in PM/DM worsening

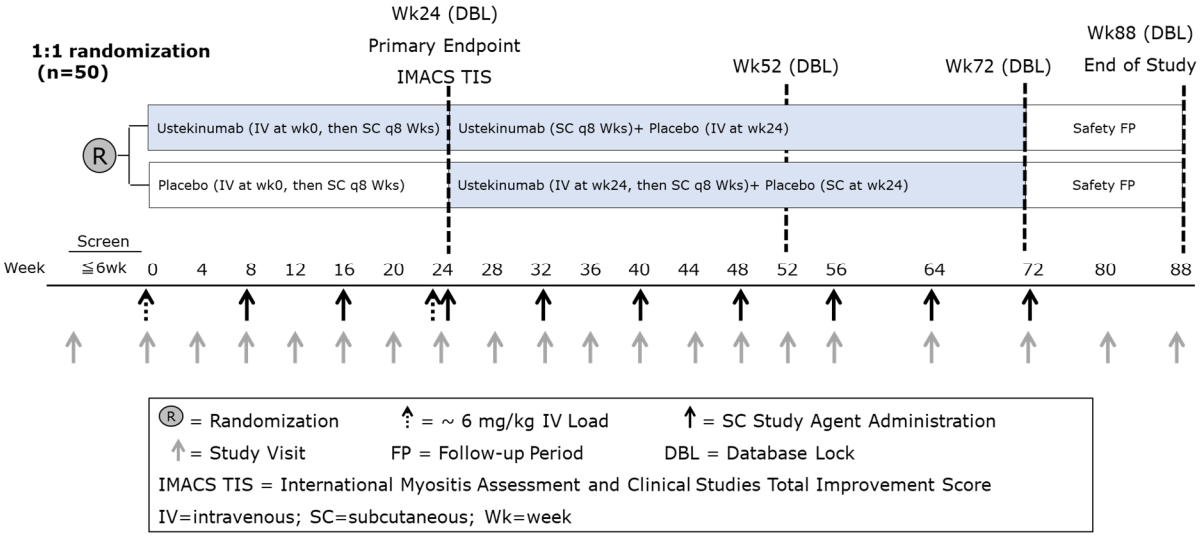
Tertiary Objectives

The tertiary objectives are to evaluate:

- Safety and tolerability
- Pharmacokinetics (PK) and immunogenicity
- Pharmacodynamic and response biomarkers of ustekinumab treatment
- Effect on health-related quality of life and physical function

1.2. Trial Design

Figure 1 Schematic overview of the study design



This is a randomized, double-blind, placebo-controlled, multicenter, interventional study in participants ≥18 years and ≤75 years of age with active PM/DM despite receiving 1 or more standard-of-care treatments (eg, glucocorticoids and/or immunomodulators) to evaluate the efficacy, safety, and tolerability of ustekinumab in addition to standard-of-care background therapy.

The total duration of the study is up to 94 weeks, consisting of 3 study periods: a ≤6-week screening period (rescreening is permitted once per participant), a 72-week study drug administration period, and 16-week follow-up period.

Key features of study drug administration for each treatment group are outlined below:

Week 0 through Week 24 (Blinded Treatment Period)

As depicted in Figure 1, approximately 50 subjects who satisfy all inclusion and exclusion criteria will be randomized in a 1:1 ratio to one of two arms:

- **Group I** (n=25): body weight-range based intravenous (IV) administration of ustekinumab (~6 mg/kg, ustekinumab 260 mg weight ≤55 kg; ustekinumab 390 mg weight >55 kg and ≤85 kg; ustekinumab 520 mg weight >85 kg) at Week 0, and ustekinumab 90 mg SC administration at Week 8 and 16.
- **Group II** (n=25): IV dosing of placebo at Week 0 followed by placebo SC administration at Week 8 and 16.

Subject will be assigned to 1 of 2 treatment groups using a stratified block randomization method in a 1:1 ratio at Week 0. Stratification factors will be disease subset (PM/DM) and baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]).

After Week 24 until Week 72 (Cross-over administration Period)

The observational period will begin from Week 24 and extend until Week 72. All subjects will receive active treatment. There will be 16 weeks safety follow-up after Week 72.

Treatment code will not be revealed to the investigators and subjects until the last subject has completed the Week 88 visit. The end of the study is defined as the time the last subject completes the Week 88 visit. Database locks will occur at Weeks 24, 52, 72 and 88. Another additional database lock will occur when 20 subjects complete 24-week evaluation for the interim analysis and analyses for the interim analysis will be detailed in a separate document.

- **Group I** (n=25): placebo IV and ustekinumab 90 mg SC administration at Week 24, and ustekinumab 90 mg SC administration thereafter through Week 72.
- **Group II** (n=25): body weight-range based IV administration of ustekinumab (~6 mg/kg) and placebo SC at Week 24, and ustekinumab 90 mg SC administration thereafter through Week 72.

1.3. Statistical Hypotheses for Trial Objectives

This study is designed to show that treatment effect (as measured by the IMACS TIS response at Week 24) of ustekinumab as PM/DM treatment is superior to placebo.

If OR is the odds ratio derived from the IMACS TIS response with the placebo and an ustekinumab groups, then the hypothesis can be written as follows:

$$H_0: OR=1,\ H_1: OR\neq 1$$

1.4. Sample Size Justification

The sample size calculation is based upon the primary endpoint, the proportion of participants who achieve IMACS TIS response at Week 24. To determine the effect size versus placebo used for calculating the sample size, meta-analyses were conducted for the synthesis of the evidence. Considering the primary endpoint evaluated at Week 24 in Japanese patients, a dropout rate of 5% is accommodated for sample size calculation. Particularly focusing on the effect size of 40% which is considered a reasonable estimate of effect size, a sample size of 50 participants is projected to give 82.2% power to detect a significant difference in response rate compared with placebo (assuming 25% and 65% response rates in placebo and ustekinumab, respectively with the 5% dropout rate in 24 weeks, which translates to 40% absolute increase over placebo or an odds ratio of 5.57) with an alpha level of 0.05 (2-sided).

1.5. Randomization and Blinding

Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by disease subset (PM/DM) and baseline

treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the study drug assignment and matching study drug kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the study drug by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

In this study, 4 DBLs are planned. These are DBLs at Week 24, Week 52, Week 72, and Week 88. In addition to these 4 DBLs, one DBL will occur for the interim analysis of futility. After Week 24, participants who are randomized to placebo group will crossover to receive ustekinumab and all the participants will enter the cross-over administration phase to allow for evaluation of the long-term efficacy and safety of ustekinumab. Investigative study sites and participants will remain blinded to initial treatment assignment until after the DBL at Week 52. After the Week 24 DBL, the data will be unblinded to sponsor for analysis while investigational sites and participants are still participating in the study. Identification of sponsor personnel who will have access to the unblinded participant data during the period from the Week 24 DBL to the Week 52 DBL will be documented prior to unblinding to sponsor.

1.6. Coronavirus 2019 (COVID-19)

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study

site personnel being reassigned to critical tasks. More details about study operational procedures related to COVID-19 are described in the COVID-19 Appendix to the study protocol.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses. The study visits scheduled after randomization should occur at the times delineated in the Time and Events Schedule of the protocol. If the certain visit occurs greater than 8 weeks of the scheduled visit, or cumulative out of visit window weeks until certain visit are greater than 16 weeks of the scheduled visits, then all measurements will be treated as missing starting from that visit to Week 24.

2.2. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled for analyses.

2.3. Analysis Sets

2.3.1. Enrolled Analysis Set

The enrolled analysis set includes all subjects who signed the ICF.

2.3.2. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study, namely intent-to-treat (ITT).

In the demographics and disposition analyses, subjects will be analyzed according to their assigned treatment group. On the other hand, in the efficacy analyses, subjects will be analyzed according to their assigned treatment group regardless of their actual treatment received.

2.3.3. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose (partial or complete, IV or SC) of study agent.

In the safety analyses, subjects will be analyzed according to the actual treatment received. Randomized subjects confirmed not to have taken any study medication will not be included in the safety analysis set.

2.3.4. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set is defined as subjects who have received at least 1 complete dose of ustekinumab and have at least one valid blood sample drawn for PK analysis.

In the PK analyses, subjects will be analyzed according to the actual treatment received.

2.3.5. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least 1 dose (partial or complete, IV or SC) of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 appropriate sample obtained after their first dose of ustekinumab).

In the immunogenicity analyses, subjects will be analyzed according to the actual treatment received.

2.3.6. Pharmacodynamics Analysis Set

The pharmacodynamic analysis set is defined as all subjects who have received at least 1 dose (partial or complete) of ustekinumab.

2.3.7. Pharmacokinetics/Pharmacodynamics Analysis Set

The pharmacokinetics/pharmacodynamics (PK/PD) analysis set is defined as all subjects (including participants who received placebo intervention) who have at least 1 paired PK and PD data collected at same time point needed for each PK/PD analysis. If participants who receive placebo intervention and have no concentration data before Week 24 visit, serum ustekinumab concentrations will be imputed as zero and should be included into PK/PD analyses through Week 24 as well.

2.4. Analysis Periods and Treatment Groups

Four database locks (DBLs) will occur at Week 24, Week 52, Week 72, and Week 88. Based on the study design features, the following analysis periods and treatment groups are defined to analyze the data according to the data collection type.

All the data collected only at Screening and/or Baseline (eg, demographic, medical history), will be included in Week 24 DBL report.

Visit-by-visit data

Hereinafter in this document, visit-by-visit data is referred as those data which are collected at specified visits in the Time and Events Schedule of the protocol, such as, efficacy assessments, vital signs, 12-lead ECG, laboratory assessments and PK and Immunogenicity assessments.

From Week 0 through Week 24

- Analyses of efficacy endpoints for placebo comparison through Week 24 will be based on the all randomized analysis set and will be summarized by the following treatment groups:
    - Placebo: Subjects randomized to Placebo group at Week 0
    - Ustekinumab: Subjects randomized to Ustekinumab at Week 0

- Analyses of safety endpoints through Week 24 will be based on the safety analysis set and will be summarized by the following treatment groups:
  - Placebo: Subjects received Placebo at Week 0
  - Ustekinumab: Subjects received Ustekinumab at Week 0
- Analyses of PK endpoints through Week 24 will be based on the PK analysis set and will be summarized by the following treatment groups:
  - Placebo: Subjects received Placebo at Week 0
  - Ustekinumab: Subjects received Ustekinumab at Week 0
- Analyses of immunogenicity endpoints through Week 24 will be based on the immunogenicity analysis set and will be summarized by the following treatment groups:
  - Placebo: Subjects received Placebo at Week 0
  - Ustekinumab: Subjects received Ustekinumab at Week 0
- Analyses of PK/PD endpoints through Week 24 will be based on the PK/PD analysis set and will be summarized by the following treatment groups:
  - Placebo: Subjects received Placebo at Week 0
  - Ustekinumab: Subjects received Ustekinumab at Week 0

<u>From Week 24 through Week 52/72/88</u>

- Analyses of efficacy endpoints from Week 24 through Week 52/72/88 will be based on the all randomized analysis set and will be summarized by following treatment groups:
  - Placebo -> Ustekinumab: Subjects randomized to Placebo group at Week 0 and then cross over to receive Ustekinumab at Week 24
  - Ustekinumab: Subjects randomized to Ustekinumab at Week 0 and continue receiving Ustekinumab throughout the study
- Analyses of safety endpoints from Week 24 through Week 52/72/88 will be based on the safety analysis set and will be summarized by following treatment groups:
  - Placebo -> Ustekinumab: Subjects received Placebo at Week 0 and then cross over to receive Ustekinumab at Week 24
  - Ustekinumab: Subjects received Ustekinumab at Week 0 and continue receiving Ustekinumab throughout the study
- Analyses of PK endpoints from Week 24 through Week 52/72/88 will be based on the PK analysis set and will be summarized by following treatment groups:
  - Placebo -> Ustekinumab: Subjects received Placebo at Week 0 and then cross over to receive Ustekinumab at Week 24
  - Ustekinumab: Subjects received Ustekinumab at Week 0 and continue receiving Ustekinumab throughout the study

- Analyses of immunogenicity endpoints through Week 52/72/88 will be based on the immunogenicity analysis set and will be summarized by the following treatment groups:
  - Placebo -> Ustekinumab: Subjects received Placebo at Week 0 and then cross over to receive Ustekinumab at Week 24
  - Ustekinumab: Subjects received Ustekinumab at Week 0 and continue receiving Ustekinumab throughout the study
- Analyses of PK/PD endpoints from Week 24 through Week 52/72/88 will be based on the PK/PD analysis set and will be summarized by following treatment groups:
  - Placebo -> Ustekinumab: Subjects received Placebo at Week 0 and then cross over to receive Ustekinumab at Week 24
  - Ustekinumab: Subjects received Ustekinumab at Week 0 and continue receiving Ustekinumab throughout the study

2.5. Data cut-off for Week 24, 52 and 72

The selections of data to be included in the analysis period through Week 24/52/72 will be done by determining a patient specific Week 24/52/72 cut-off date and including all data measured and observed up to this cut-off date in the Week 24/52/72 analyses. The patient specific cut-off date is defined as:

Scenarios	Patient specific cut-off date
Patients had Week 24/52/72 visit	Use Week 24/52/72 visit date
Patients discontinued prior to Week 24/52/72	No cut-off date and include all their data in Week 24/52/72 analyses
Patients had no Week 24/52/72 visit and did not discontinue prior to Week 24/52/72	Use last visit date up to study day 182/378/523 relative to the first stud agent administration for Week 24/52/72 respectively

2.6. Definition of Subgroups

Subgroup analysis of the primary endpoint based on the following baseline characteristics may be performed:

Subgroup	**Definition**
Disease subset	• PM • DM
Baseline treatment level of glucocorticoid dose	• ≥0.5 mg/kg/day of prednisolone or equivalent • <0.5 mg/kg/day of prednisolone or equivalent
Age Group	• [<65] • [≥65]
BMI	• [<18.5 kg/m^2] • [18.5-<25.0 kg/m^2] • [≥25.0 kg/m^2]
Sex	• Male • Female
ILD at baseline	• ILD at baseline • No ILD at baseline

2.7. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration or randomization date if subject was never dosed. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1

There is no 'Day 0'.

2.8. Baseline

Baseline is defined as the last observation prior to the start of the first study agent administration. Baseline immunomodulator/glucocorticoid dose is defined as the daily dose on Study day -1 (the day before randomization).

2.9. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the study agent start date
  - The time of the study agent start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Details of the Data Monitoring Committee (DMC) safety reviews and interim analysis assessments are included in a separate DMC Charter and DMC SAP. The DMC SAP contains definitions of analysis sets, statistical methods, and data presentation specifications used for safety data review and interim analysis.

The following offers a high-level summary of Interim Analysis and DMC review activities.

3.1. Interim Analysis

An interim analysis is planned with the objective of stopping the study for futility. It is scheduled when approximately 40% of the 50 randomized subjects (20 patients) have completed Week 24 visit or have ended study participation before Week 24 visit. Data, statistical methods, decision rules regarding futility stopping, and mockup tables, listings, and graphs used in the interim analysis, are specifically described in DMC SAP.

3.2. Data Monitoring Committee Review

The independent DMC will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. The committee will periodically review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. Any safety concerns will be communicated to the Sponsor.

None of the DMC members will be participating in the study; they will be independent of the Sponsor. The independent DMC consists of at least 2 medical experts in relevant therapeutic areas and 1 statistician and are to be specified before study initiation. The major function of the DMC is to monitor the safety of the study agent by reviewing the SAE and unblinded safety data every 2

months, and to review unblinded results of interim efficacy analysis in addition to ongoing safety review.

The content of the safety summaries and interim analysis, the DMC roles and responsibilities and the general procedures (including communication plan) and their possible recommendations on study conduct are defined and documented in the DMC Charter prior to the first DMC review.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group, and overall.

4.1. Demographics and Baseline Characteristics

Table 1 presents a list of the demographic variables that will be summarized by treatment group, and overall for the all randomized analysis set. Prior and concomitant medications used at baseline will be listed.

Table 1: Demographic Variables and Disease Characteristics at Baseline

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Disease duration (years)	
PhGA of disease activity (100 mm)	
PtGA of disease activity (100 mm)	
MMT-8 (0-80)	
Creatine Kinase (CK) (IU/L)	
Alanine Aminotransferase (ALT) (IU/L)	
Aspartate Aminotransferase (AST) (IU/L)	
Lactate Dehydrogenase (LDH) (IU/L)	
Aldolase (IU/L)	
Manual Muscle Testing (MMT)-8	
MDAAT-Extramuscular Global Assessment (100 mm)	
HAQ-DI (1-3)	
SF-36 mental	
SF-36 physical	
Categorical Variables	
Age (<65 years and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race (Asian)	
BMI (<18.5 kg/m^2, 18.5-<25.0 kg/m^2, ≥25.0 kg/m^2)	
Diagnosis (PM, DM)*	
ILD at baseline (Yes, No)	
Glucocorticoid at baseline (≥0.5 mg/kg/day of prednisolone or equivalent , <0.5 mg/kg/day of prednisolone or equivalent) *	

*Diagnosis and Glucocorticoid at baseline will be based on the eCRF page of "PM/DM classification European League Against Rheumatism/American College of Rheumatology Classification Criteria" and "Glucocorticoid Therapy".

4.2. Disposition Information

Disposition information will be based upon the randomized analysis set.

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall for 4 analysis periods: through Week 24, through Week 52, through Week 72, through end of study.

- Subjects with informed consent
- Subjects with screening failure
- Subjects randomized
- Subjects receiving study agent
- Subjects completing the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

Completion status of study agent through Week 24 and through Week 52 is not captured in eCRF and will be defined as follows:

- A patient will be considered a Week 24/52 completer if the patient: 1) has Week 24/52 visit, or 2) has no Week 24/52 visit but has not discontinued from the treatment before or on Week 24/52 cut-off date (ie, no discontinuation is reported or discontinuation is reported on the eCRF page of "END OF TREATMENT" but with a Treatment Disposition Date greater than Week 24/52 cut-off date).
- A patient will be considered as a Week 24/52 non-completer if the patient has no Week 24/52 visit and discontinued from the treatment before Week 24/52 cut-off date (ie, discontinuation is reported on the eCRF page of "END OF TREATMENT" with a Treatment Disposition Date before Week 24/52 cut-off date).

4.3. Treatment Compliance

The study drug will be administered as an IV infusion or SC by qualified study site personnel and the details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, and volume infused). Compliance with the treatment assignments will be controlled by the study site personnel.

Study agent compliance will be summarized descriptively. Compliance to randomized treatment versus actual treatment through Week 24 will be presented in a summary table.

4.4. Extent of Exposure

The number of subjects exposed to study agent, the number of administrations of study agent by type of administration (IV and SC), and cumulative dose (IV and SC) of study agent will be summarized by treatment group.

Analysis periods and treatment groups described for summary data in Section 2.4 will also be applied to the exposure data.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

Analysis periods and treatment groups defined in Section 2.4 will be applied for the above analyses.

4.6. Prior and Concomitant Medications

Background therapy for active PM/DM summarized by treatment group may be provided.

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent.

Prior medications and concomitant medications will be summarized respectively by treatment group and ATC term.

4.7. COVID-19 Related Summaries

Depending on the COVID-19 impact on this study, the following summarizes may be provided.

Subject disposition as related to COVID-19 may be summarized by treatment group. This includes the following COVID-19 related disposition events:

- Termination of study due to COVID-19 and reason
- Discontinuation of study agent due to COVID-19 and reason
- Death related to COVID-19

Subjects discontinuing treatment or terminating study participation due to COVID-19 and reason(s) may be listed.

Concomitant medications used for COVID-19 may be summarized. Subjects receiving concomitant medications related to COVID-19 may be listed.

Protocol deviations (major and minor) as related to COVID-19 may be summarized and listed.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise stated, the statistical significance is set to 2-sided α-level of 0.05 as per protocol. When appropriate, 95% confidence intervals will be provided.

5.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who achieve IMACS TIS response at Week 24.

5.2.1. Definition

The IMACS TIS (Total Improvement Score) ranges from 0 to 100. This score is the sum of the 6 IMACS core set measures as follows:

- PhGA of disease activity
- PtGA of disease activity
- MMT-8
- Physical Function (HAQ-DI)
- Muscle Enzymes
- Extramuscular Assessment (MDAAT)

The absolute percent change is calculated for each core set measure.

$$Absolute\ percent\ change = \frac{(final\ value) - (baseline\ value)}{range} \times 100$$

The thresholds of improvement and improvement score are summarized in the table for each core set (Table 2). The total improvement score is calculated by sum of 6 core set improvement scores. The total improvement score is categorized into 3 categories (minimal, moderate and major) (Table 3). The IMACS TIS response as the primary endpoint is defined as IMACS TIS ≥ 20 (minimal) (Aggarwal 2017).

Table 2: The Thresholds of Improvement and Improvement Score

Core Set Measure	Level of Improvement Based on absolute percentage change	Improvement Score
PhGA of disease activity	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
PtGA of disease activity	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 or Childhood Myositis Assessment Scale (MMT-8)	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
(Childhood) Health Assessment Questionnaire (HAQ-DI)	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 (most abnormal) (Muscle Enzymes)	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 Activity or Disease Activity Score (MDAAT)	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

Table 3: Criteria for Minimal, Moderate, and Major Clinical Response

	Improvement Category	Total Improvement Score
PM/DM thresholds	Minimal	≥ 20
	Moderate	≥ 40
	Major	≥ 60

5.2.1.1.1. Physician Global Activity (PhGA)

This is the assessment by the treating physician to measure the global evaluation of the patient's overall disease activity using a 10 cm VAS. Left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity. [range: 10 cm]

5.2.1.1.2. Patient Global Activity (PtGA)

This is the assessment by the patient to measure the global evaluation of the patient's overall disease activity using a 10 cm VAS. Left end of line = no evidence of disease activity, and right end of line = extremely active or severe disease activity. [range: 10 cm]

5.2.1.1.3. Manual Muscle Testing (MMT-8)

MMT-8 is a set of 8 designated muscles tested unilaterally, generally on right side (unless cannot be tested on right, then use left side) The evaluation is considered as improvement with higher score [range: 80].

The side (right or left) used for calculating the total score at baseline and post-baseline should be consistent within each muscle group. Muscle groups with both sides scored at baseline, unless there are more missing values on right side scores, then the left side scores should be used.

MMT-8 total score will be calculated only if at least 4 muscle groups can be scored (ie, nonmissing). When at least 4 muscle groups can be scored, missing muscle groups will be imputed by the closet previous nonmissing values. If less than 4 muscle groups can be scored, then MMT-8 total score will be considered as missing.

5.2.1.1.4. Physical Function (HAQ-DI)

The functional status of the subject is evaluated by HAQ disability index (HAQ-DI) score (Fries 1980; Matsuda 2003). The HAQ-DI is composed of eight categories: dressing (C1), arising (C2), eating (C3), walking (C4), hygiene (C5), reaching (C6), gripping (C7) and activities of daily living (C8). For each of these categories, subjects are asked to record the amount of difficulty they may have in performing various activities. The possible answers for the component questions are shown in Table 4.

Table 4: The possible answers for the component questions and corresponding scores

Answer to the component question	Score
Without ANY difficulty	0
With SOME difficulty	1
With MUCH difficulty	2
UNABLE To Do	3

The highest score recorded by the subject for any component question determines the score for that category. Subjects are also asked to indicate their use of any AIDS OR DEVICES or if they need help from another person for any of these activities. And the component score is adjusted based on the subject's use of any Aid or Device or assistance from any other person for that component.

If Aid or Devices and/or help from another person is checked for a category, the score is set to "2", unless the score is already "3" (i.e., scores of "0" or "1" are increased to "2").

The disability index is calculated as the sum of computed component scores (the highest scores in each category) divided by the number of categories answered. The disability index is not computed if the subject does not have scores for at least 6 categories of the 8 categories.

$$\text{HAQ} - \text{DI score} = \frac{sum\ of\ the\ highest\ scores\ in\ each\ category}{The\ number\ of\ categories\ answered}$$

The pre-specified devices for the above stated categories are summarized in Table 5.

Table 5: The pre-specified devices and the corresponding category

Category	Name of Category	Devices
C1	Dressing	Devices used for dressing (button hook, Zipper pull, long-handled show horn, etc.)
C2	Arising	Special or built up chair
C3	Eating	Built up or special utensils
C4	Walking	Cane, Walking Frame, Crutches, Wheelchair
C5	Hygiene	Raised toilet seat. Bathtub seat, Bathtub bar, Long-handled appliances in the bathroom
C6	Reaching	Long-handled appliances for reach
C7	Gripping	Jar opener (for jars previously opened)

The pre-specified help from another person for the above stated categories are summarized in Table 6.

Table 6: The pre-specified help from another person and the corresponding category

Category	Name of Category	Help from another person
C1	Dressing	Dressing and grooming
C2	Arising	Arising
C3	Eating	Eating
C4	Walking	Walking
C5	Hygiene	Hygiene
C6	Reaching	Reach
C7	Gripping	Gripping and opening things
C8	Activities	Errands and chores

The aids or devices other than the ones specified in the table above will be recorded in the "Other (Specify)" section. Aids or Devices written in the "Other (Specify)" sections or notes written next to any component questions are considered if they could be classified to any of the stated categories.

5.2.1.1.5. Muscle Enzymes

For muscle enzymes, the most abnormal enzyme at baseline is used. The most abnormal enzyme is determined by having the greatest baseline divided by its upper limit of normal. However, if the value at Week 24 for the most abnormal enzyme at baseline is missing but the values at Week 24 for other enzymes are not missing, the other enzyme will be used to calculate the IMACS TIS score by the order of degree of abnormality. The values obtained from central laboratory are used for evaluation. The enzyme range was calculated based on 90% range of enzymes from natural history data (Table 7).

$$Absolute\ percent\ change = \frac{(final\ value) - (baseline\ value)}{90\%\ range} \times 100$$

Table 7: Muscle enzyme and its range by adults/juveniles

Adults/Juveniles	Muscle enzyme	90% range
Adults	CK (creatine kinase)	$15 \times (the\ upper\ limit\ of\ normal)$
	Aldolase	$6 \times (the\ upper\ limit\ of\ normal)$
	LDH (lactate dehydrogenase)	$3 \times (the\ upper\ limit\ of\ normal)$
	AST (aspartate aminotransferase)	$3 \times (the\ upper\ limit\ of\ normal)$
	ALT (alanine aminotransferase)	$3 \times (the\ upper\ limit\ of\ normal)$
Juveniles	CK (creatine kinase)	$20 \times (the\ upper\ limit\ of\ normal)$
	Aldolase	$6 \times (the\ upper\ limit\ of\ normal)$
	LDH (lactate dehydrogenase)	$5 \times (the\ upper\ limit\ of\ normal)$
	AST (aspartate aminotransferase)	$5 \times (the\ upper\ limit\ of\ normal)$
	ALT (alanine aminotransferase)	$5 \times (the\ upper\ limit\ of\ normal)$

5.2.1.1.6. Extramuscular Assessment (Myositis Disease Activity Assessment Tool)

This is the assessment using a 10 cm VAS. Left end of line = no evidence of disease activity, and right end of line = extremely active or severe disease activity. The extramuscular assessment VAS is used for calculation of IMACS TIS. [range: 10 cm]

Apart from the extramuscular assessment VAS, MDAAT is measured. The MDAAT is a combined tool that includes the Myositis Disease Activity Assessment VAS (MYOACT) and the Myositis Intention to Treat Activity Index (MITAX). MYOACT and MITAX score will be calculated only if >= 50% of used organ systems can be scored. If < 50% of used organ systems are scored, MYOACT and MITAX score will be considered missing. Note that if the MITAX category score or VAS for one organ system cannot be assessed, both of them will be considered not assessed.

Myositis Disease Activity Assessment (MYOACT): The MYOACT is the sum of the 10 cm VAS scores for each of the six individual organ systems (Constitutional, Cutaneous, Skeletal, Gastrointestinal, Pulmonary, Cardiac) and divided by the total possible score (range = 60). If one or more organ systems were not assessed, the resulting score would be divided by the maximum possible score from those assessed items (Whiting 1999). For example, if Constitutional VAS = 8, Cutaneous VAS = 6, Skeletal VAS = not scored, Gastrointestinal VAS = not scored, Pulmonary VAS = 1, Cardiovascular VAS = not scored, then MYOACT score = (8+6+1) / 10*3 = 0.5.

Myositis Intention to Treat Activity Index (MITAX):

The MITAX is scored on a 0 to 4 scale, based on worsening or improvement in specific clinical features and their correlation with the intention to treat (Hay 1993).

The MITAX score is the sum of the worst category scores for each of the seven individual organ systems (Constitutional, Cutaneous, Skeletal, Gastrointestinal, Pulmonary, Cardiac, Muscle) divided by the maximum possible score (range = 1 – 63). If one or more organ systems were not assessed, the score would be calculated by dividing the sum by the maximum possible score of the assessed organ systems. For example, if Constitutional = category A (9 points), Cutaneous = category B (3 points), Skeletal = not scored, Gastrointestinal = not scored, Pulmonary = category C (1 point), Cardiovascular = category D (0 point), Muscle = category B (3 points), then MITAX score = (9+3+1+0+3) / 9*5 = 0.3556.

Score	Symptoms
0	If the feature is not present
1	If the feature is improving – clinically significant improvement in the last 4 weeks over the previous 4 weeks
2	If the feature is the same – manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration
3	If the feature is worse – clinically significant deterioration over the last 4 weeks compared to the previous 4 weeks
4	If the feature is new – new in the last 4 weeks (compared to the previous 4 weeks)
NA	If the feature cannot be assessed

As the table below shows, each organ system of the MITAX is scored by selecting the highest category selected for any of the individual items under that organ system (ie, the worse item carries the score for the organ system). Whether NA (Not Assessed) or not for each organ system should be judged by whether all items used in category A are not NA. If judged to be "Not NA", the system organ will be scored in an order of Category A→B→C→E→D. Only if all Category A, B and C are not scored, Category D or E will be scored. Whether Category D or E will be determined by the presence of previous activity (Y/N). If all previous scores for this organ system are D or E or NA, then this organ system should be scored as E; otherwise scored as D. Screening assessments will be used as previous activity for baseline.

If without ILD, Category A for the pulmonary organ system will be evaluated with item 17a, 17b and 19; if with ILD, this score will be evaluated with item 18a, 18b, 18c and 19. Since chest x-ray, HRCT and FVC tests are not performed every 4 weeks, the values for these assessments obtained within 13 weeks before the visit are allowed to be used for evaluating item 18b and 18c. At baseline, because 18c is scored as NA, only 18a and 18b will be used for pulmonary organ system scoring. At Week 24 (primary endpoint), all 3 items of 18a, 18b and 18c will be used.

	CATEGORY A **A = Active** **(9 points)**	**CATEGORY B** **B = Beware** **(3 points)**	**CATEGORY C** **C = Contentment** **(1 point)**	**CATEGORY D** **D = Discount** **(0 points)**	**CATEGORY E** **E = No evidence** **(0 points)**
Constitutional Disease Activity	Pyrexia (item 1) scoring 2, 3 or 4 **plus** two other clinical feature scoring > 1: -Unintentional weight loss (item 2) -Fatigue/malaise/lethargy (item 3)	Any one clinical feature scoring 2, 3 or 4	Any one clinical feature scoring 1	No current activity but known to have been active in the past. - ie remission	No current or previous activity.
Cutaneous Disease Actlvity	Any one of the following scoring 2, 3 or 4: -Cutaneous ulceration (item 4) -Erythroderma (item 5) -Erythematous rashes with secondary changes eg. accompanied by vesiculobullous or erosive changes or necrosis (item 7a) -Panniculitis (item 6)	1) Any Category A clinical feature scoring 1 **OR** 2) Any one of the following scoring 2, 3 or 4: -Erythematous rashes without secondary changes (item 7b) -Heliotrope rash (item 8) -Gottron's papules or sign (item 9) -Periungual capillary changes (item 10) -Alopecia: diffuse (item 11a) -Mechanic's hands (item 12)	1) Any Category B clinical feature scoring 1 **OR** 2) Alopecia: focal (item 11b) - scoring 1, 2, 3 or 4	No current activity but known to have been active in the past. - ie remission	No current or previous activity.
Skeletal Disease Activity	Severe inflammatory polyarthritis (item 13a) scoring 2, 3 or 4	1) Severe inflammatory polyarthritis scoring 1 (item 13a) **OR** 2) Moderate inflammatory arthritis (item 13b) scoring 2, 3 or 4	1) Any category B clinical feature scoring 1 **OR** 2) Any one of the following scoring 1, 2, 3 or 4: -Mild arthritis (item 13c) -Arthralgia (item 14)	No current activity but known to have been active in the past. - ie remission	No current or previous activity.
Gastrointestinal Disease Activity	Any one of the following scoring 2, 3 or 4: -Moderate to severe dysphagia (item 15a) -Severe abdominal pain (item 16a)	1) Any Category A clinical feature scoring 1 **OR** 2) Any one of the following scoring 2, 3 or 4 -Moderate abdominal pain (item 16b) -Mild dysphagia (item 15b)	1) Any Category B clinical feature scoring 1 **OR** 2) Mild abdominal pain (item 16c) scoring 1, 2, 3 or 4	No current activity but known to have been active in the past. - ie remission	No current or previous activity

Pulmonary Disease	1)Ventilatory abnormalities due to muscle weakness without primary lung disease- dyspnea at rest scoring 2, 3, or 4 (item 17a) **OR** 2)Active ILD scoring 3 (worse) or 4 (new) **in at least two** of the following: a) dyspnea or cough due to ILD (item 18a) b) parenchymal abnormalities on CXR or HRCT and/or ground glass-shadowing (item 18b) c) PFTs - minimum of 10% change in FVC or 15% change in DLCO (item 18c)	1) 17a) scoring 1, OR Ventilatory abnormalities due to muscle weakness without primary lung disease - Dyspnea on exertion scoring 2, 3, or 4 (item 17b) 2) Active ILD scoring 2 (same) in at least two of the following (or scoring 1 or 3 in only one category with 2 in others) a) dyspnea or cough due to ILD (item 18a) b) parenchymal abnormalities on CXR or HRCT and/or ground glass-shadowing (item 18b) c) PFTs - minimum of 10% change in FVC or 15% change in DLCO (item 18c) 3) Moderate to severe dysphonia scoring 2, 3 or 4 (item 19a)	1) 17 b scoring 1 OR Active ILD scoring 1 (ie improvement) in at least two of the following: a) dyspnea or cough due to ILD (item 18a) b) parenchymal abnormalities on CXR or HRCT and/or ground glass-shadowing (item 18b) c) PFTs - minimum of 10% change in FVC or 15% change in DLCO (item 18c) 2) Moderate to severe dysphonia scoring 1 (item 19a) OR Mild dysphonia scoring 1, 2, 3 or 4 (item 19b)	No current activity but known to have been active in the past - ie remission	No current or previous activity
Cardiovascular Disease Activity	Any one of the following scoring 2, 3 or 4 -Myocarditis (item 21)/pericarditis (item 20) -Severe cardiac arrhythmia (item 22a)	1) Any Category A clinical feature scoring 1 **OR** 2) Any one of the following scoring 2, 3 or 4: -Mild/moderate cardiac arrhythmia (except sinus tachycardia) (item 22b)	1) Any Category B clinical feature scoring scoring 1 **OR** 2) Sinus tachycardia scoring 1, 2, 3 or 4 (item 23)	No current activity but known to have been active in the past - ie remission	No current or previous activity
Muscle Disease Activity	Myositis resulting in severe muscle inflammation (item 25a) scoring 2, 3 or 4	1) Severe muscle inflammation (item 25a) scoring 1, **OR** 2) Moderate muscle inflammation (item 25b) scoring 2, 3, or 4	1) Myositis resulting in moderate inflammation (item 25b) scoring 1, **OR** 2) Myositis resulting overall in mild inflammation (item 25c) scoring 1, 2, 3 or 4 3) Myalgia scoring (item 26) scoring 1, 2, 3 or 4	No current activity but known to have been active in the past - ie remission	No current or previous activity

5.2.2. Estimands

5.2.2.1. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of ustekinumab in participants with active PM/DM despite receiving 1 or more standard-of-care treatments (eg, glucocorticoids and/or immunomodulators).

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from ustekinumab vs placebo for the pre-specified duration (24 weeks), administered together with the protocol allowed 1 or more standard-of-care treatments?

The **Primary Estimand** will be targeted for the primary endpoint. The Primary Estimand for the primary endpoint is defined by the following:

- **Study intervention:**
  - Ustekinumab (~6 mg/kg IV at Week 0, and 90 mg SC q8w through Week 24)
  - Placebo (IV at Week 0 and SC q8w through Week 24)
- **Population:** Subjects with active PM/DM despite receiving one or more standard-of-care treatments.
- **Variable/endpoint:** IMACS TIS binary response variable at Week 24, where a responder is defined as a participant who achieves IMACS TIS response at Week 24 and does not have a prohibited change in PM/DM medications (for details, see Appendix 1). A participant who has a prohibited change in PM/DM medications or discontinues treatment for any reason including COVID-19 infection but excluding other COVID-19 reasons is considered a non-responder.
- **Population-level summary:** Odds ratio for the proportion of subjects achieving IMACS TIS response at Week 24 between the ustekinumab and placebo intervention groups.
- **Intercurrent events (ICEs) and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Composite Strategy:** A subject with this intercurrent event is considered as a non-responder after this event, the occurrence of this intercurrent event being captured in the variable definition.
2. Discontinuation of study intervention for any reason, including COVID-19 infection but excluding other COVID-19 reasons	
3. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)	**Hypothetical Strategy:** This intercurrent event is addressed with a hypothetical strategy, as if the intercurrent event would not have occurred.

For subjects experiencing multiple ICEs simultaneously, ICEs in categories 1- 2 will override ICE 3.

5.2.2.2. Supplementary Estimands

Supplementary Estimand 1 (Hypothetical Estimand)

Estimand Scientific Question of Interest: If participants are compliant with the investigative therapy, what is the proportion of participants considered to have benefited from ustekinumab vs placebo for the pre-specified duration (24 weeks), administered together with the protocol allowed background standard-of-care medication?

Hypothetical estimand is defined to support the primary estimand.

- **Study intervention and Population:** Same attributes as primary estimand.
- **Variable:** IMACS TIS binary response variable at Week 24, where a responder is defined as a subject who achieves IMACS TIS response at Week 24
- **Summary Measure (Population-level summary):**

  Odds ratio for the proportion of subjects achieving IMACS TIS response at Week 24 between the ustekinumab and placebo treatment groups.

- **Intercurrent events and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Hypothetical Strategy:** This intercurrent event is addressed with a hypothetical strategy, as if the intercurrent event would not have occurred.
2. Discontinuation of study intervention for any reason	

Supplementary Estimand 2 (Treatment Policy Estimand):

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from ustekinumab vs placebo for the pre-specified duration (24 weeks), administered together with the protocol allowed background standard-of-care medication, regardless of initiation/adjustment of concomitant medication or discontinuation of study intervention?

Treatment policy estimand is defined to support the primary estimand.

- **Study intervention and Population:** Same attributes as primary estimand.
- **Variable:** IMACS TIS binary response variable at Week 24, where a responder is defined as a subject who achieves IMACS TIS response at Week 24

- **Summary Measure (Population-level summary):**

  Odds ratio for the proportion of subjects achieving IMACS TIS response at Week 24 between the ustekinumab and placebo treatment groups.

- **Intercurrent events and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this intercurrent event had occurred.
2. Discontinuation of study intervention for any reason	

5.2.3. Analysis Methods

In general, the statistical software SAS will be used for all data analysis.

Data for primary analysis

Analyses of the primary efficacy endpoint (IMACS TIS response at Week 24) will include subjects from all randomized analysis set and be based on their assigned treatment group regardless of the actual treatment received. Participants with ICEs 1-2 before Week 24 will be considered as non-responders at Week 24, as defined in the primary estimand. For participants with ICE 3, data collected after this ICE will not be utilized in the analysis. Participants who don't experience any ICEs could also have a missing value for the primary endpoint if missing the IMACS TIS response at Week 24 due to study withdrawal / missed visits or measurement.

Primary analysis method

To address the primary objective, logistic regression adjusting for 2 stratification factors (as per eCRF), disease subset (PM or DM) and baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]), will be used to analyze the primary endpoint. If the above logistic regression model does not converge, the binomial test will be conducted without adjusting for the 2 stratification factors. The magnitude of the effect will be estimated by the odds ratio in IMACS TIS response rates between the ustekinumab and placebo groups, associated 95% confidence interval (CI) and the statistical significance of the difference in treatment effect will be provided. The study will be considered positive if the proportion of IMACS TIS responders in the ustekinumab group is significantly different from placebo (2-sided p-value is less than 0.05).

The number and proportion of participants who achieve IMACS TIS composite response at Week 24 will be summarized for each treatment group. In addition, the difference in proportions will also be provided.

Missing data handling rules for primary estimand

Missing data of the primary endpoint at Week 24	Missing data handling rules
Category 1: Data on or after ICE 3 will be assumed as missing	Multiple imputation method under the assumption of missing at random, as described below.
Category 2: After accounting for the ICEs, the remaining missing data due to operational or logistical issues related to COVID-19	
Category 3: After accounting for the ICEs, the remaining missing data due to any other reasons, except for operational or logistical issues related to COVID-19	Non-responder imputation

Multiple Imputation Procedure

- Step #1: Utilize a Markov Chain Monte Carlo (MCMC) approach to impute intermediate (non-monotone) missing data for all subjects. Perform 500 imputations (seed=127501) to create 500 unique datasets now having monotone missing data patterns. As the endpoint is binary, if the imputed value is 0.5 or above, the binary value will set to 1 (indicating response) and if the imputed value is less than 0.5, the binary value will be set to 0 (indicating non-response).
- Step #2: Utilize a monotone logistic multiple imputation method with same covariates as in the primary analysis method to impute missing data in the 500 datasets with monotone missingness. Perform the imputation (seed=127501) 1 time for each dataset resulting in 500 unique, imputed datasets (1 imputation on each of the 500 datasets created from the MCMC approach).
- Step #3: Analyze each of the 500 imputed datasets using the logistic regression model described as the primary analysis method. Utilize the SAS® MIANALYZE procedure to combine the 500 analysis results.

5.2.3.1. Subgroup Analyses

Subgroup analysis of the primary endpoint based on stratification factors (as per eCRF) will be performed. Subgroup analysis of the primary endpoint by other selected baseline characteristics may be presented when the number of subjects in the subset permits (at least 15 subjects for each treatment group within a subset):

- Disease subset (PM/DM)
- Baseline treatment level of glucocorticoid dose (≥0.5 mg/kg/day of prednisolone or equivalent, or <0.5 mg/kg/day of prednisolone or equivalent)
- Age group (<65 years and ≥65 years)
- BMI (<18.5 kg/m^2, 18.5-<25.0 kg/m^2, ≥25.0 kg/m^2)

- Sex (male, female)
- ILD at baseline (Yes, No)

The primary estimand (Section 5.2.2) will be used for these subgroup analyses and the same analysis methods defined in this section used for primary estimand will be applied. For subgroup analyses, proportion of IMACS TIS response in each treatment group, odds ratio and corresponding 95% CI will be presented. However, p-values for the comparison across treatment groups for the subgroups will not be presented. In addition, the difference in proportions will also be provided.

5.2.3.2. Sensitivity Analysis

To evaluate the robustness of the primary endpoint analysis, the following sensitivity analyses will be performed for primary estimand.

5.2.3.2.1. Sensitivity Analysis 1

Similar to the primary analysis, however baseline continuous glucocorticoid dose (as per eCRF) will be used instead of baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]) as a covariate in logistic regression model.

5.2.3.2.2. Sensitivity Analysis 2

Similar to the primary analysis, however baseline glucocorticoid daily dose (mg) as categorized by (<=15, >15) will be used instead of baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]) as a covariate in logistic regression model.

5.2.3.3. Supplementary Analyses

5.2.3.3.1. Supplementary Analysis 1 (Hypothetical Estimand)

This supplementary analysis for the primary endpoint is based on the Supplementary Estimand 1 (Hypothetical Estimand) defined in Section 5.2.2.2. Data after intercurrent events will not be utilized in the analysis, and together with missing data, these data will be imputed using multiple imputation methods (eg, multiple imputation utilized to create 500 distinct datasets, logistic regression similar to the primary analysis on each of the 500 imputed datasets and results combined to make the final inference). The imputation model will include treatment group, disease subset (PM or DM) and baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]) (as per eCRF) as covariates.

5.2.3.3.2. Supplementary Analysis 2 (Treatment Policy Estimand)

This supplementary analysis for the primary Supplementary Estimand 2 (Treatment Policy Estimand) defined in Section 5.2.2.2. For participants who experience intercurrent events through Week 24, the treatment policy strategy will be used, and the similar analysis as primary estimand will be performed using observed data regardless of intercurrent events without imputation.

5.3. Secondary Endpoints

The secondary endpoints are the following:

1. Mean change from baseline in Functional Index-2 (FI-2) at Week 24
2. The proportion of participants who experience disease worsening through Week 24 based on consensus criteria for worsening
3. Mean change from baseline in Manual Muscle Testing (MMT)-8 at Week 24
4. Mean change from baseline in PhGA of disease activity at Week 24
5. Mean change from baseline in Extramuscular Assessment (Myositis Disease Activity Assessment Tool [MDAAT]-Extramuscular Global Assessment) at Week 24
6. Mean change from baseline in muscle enzymes (creatine kinase [CK], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and aldolase) at Week 24

5.3.1. Definition

See Section 5.2.1 for the definitions of Physician Global Activity – Visual Analogue Scale, Extramuscular Assessment (MDAAT) and Muscle Enzymes.

5.3.1.1. Functional Index-2

The FI-2 is a functional outcome developed for patients with adult PM or DM to assess muscle endurance in 7 muscle groups. Each muscle group is scored as the number of correctly performed repetitions with 60 or 120 maximal number of repetitions depending on muscle group. The FI-2 is performed unilaterally, preferably on the participant's dominant side for muscle groups of shoulder, hip, and step test. The FI-2 has been validated as to content and construct validity and intra- and interrater reliability. A total score will not be calculated. For those muscle groups which can be tested bilaterally, only one side will be tested for each visit. Sides used for post-baseline assessments should be consistent with that of baseline. The values at the visits with different side from baseline for assessment will be considered as missing.

Two scales: Repetitions, % / Max Repetitions will be analyzed for each of the following FI-2 item, separately: shoulder flexion (0-60), shoulder abduction (0-60), head lift (0-60), hip flexion (0-60), step test (0-60), heel lift (0-120), toe lift (0-120).

5.3.1.2. Disease Worsening

Criteria for disease worsening in a clinical trial were based on international consensus guideline developed by the IMACS. The worsening of disease is defined as 1 of the following criteria;

1. Worsening of the Physician Global Activity by ≥2 cm on a 10-cm VAS and worsening of findings of MMT-8 by ≥20% from baseline
2. Worsening of MDAAT-global extramuscular organ disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac activity) by ≥2 cm on a 10-cm VAS from baseline

3. Worsening of any 3 of 6 IMACS core set activity measures by ≥30% from baseline

5.3.1.3. Manual Muscle Testing

Manual Muscle Testing is a partially validated tool to assess muscle strength. A 0 to 10 point scale is proposed for use. The MMT-8 is proposed for studies which evaluate 8 muscle groups whose subsets are selected based on internal/interrater consistency and reliability. The MMT-8, which take less time and involve less patient effort compared to Total MMT, has results comparable to Total MMT in terms of responsiveness, content validity, and construct validity. Analysis Methods

5.3.2. Estimands

5.3.2.1. Main Estimand for Secondary Binary Endpoint

The following describes the attributes of the estimand for the secondary binary endpoint (#2) defined in Section 5.3.1.

- **Study intervention and Population:** Same attributes as primary estimand for primary endpoint
- **Variable/endpoint and Population-level summary:**

Estimand	Variable (Endpoint)	Population-level summary
Secondary Endpoint #2 Primary Estimand	Binary variable, Disease worsening through Week 24 based on consensus criteria for worsening	Difference in percentage of subjects who experienced disease worsening through Week 24 based on consensus criteria for worsening between ustekinumab group and placebo.

- **Intercurrent events (ICEs) and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Composite Strategy:** A subject with this intercurrent event is considered as experiencing disease worsening after this event, the occurrence of this intercurrent event being captured in the variable definition.
2. Discontinuation of study intervention for any reason, including COVID-19 infection but excluding other COVID-19 reasons	
3. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this intercurrent event had occurred.

For subjects experiencing multiple ICEs simultaneously, ICEs in categories 1- 2 will override ICE 3.

5.3.2.2. Main Estimands for Secondary Continuous Endpoints

The following describes the attributes of the estimands for the secondary continues endpoints (#1, 3, 4, 5, 6) defined in Section 5.3.1.

- **Study intervention and Population:** Same attributes as primary estimand for primary endpoint
- **Variable/endpoint and Population-level summary:**

Estimand	Variable (Endpoint)	Population-level summary
Secondary Endpoint #1 Primary Estimand	Change from baseline in Functional Index-2 (FI-2) at Week 24	Difference in mean change from baseline in Functional Index-2 (FI-2) at Week 24 between ustekinumab group and placebo
Secondary Endpoint #3 Primary Estimand	Change from baseline in Manual Muscle Testing (MMT)-8 at Week 24	Difference in mean change from baseline in Manual Muscle Testing (MMT)-8 at Week 24
Secondary Endpoint #4 Primary Estimand	Change from baseline in PhGA of disease activity at Week 24	Difference in mean change from baseline in PhGA of disease activity at Week 24
Secondary Endpoint #5 Primary Estimand	Change from baseline in Extramuscular Assessment (Myositis Disease Activity Assessment Tool [MDAAT]-Extramuscular Global Assessment) at Week 24	Difference in mean change from baseline in Extramuscular Assessment (Myositis Disease Activity Assessment Tool [MDAAT]-Extramuscular Global Assessment) at Week 24
Secondary Endpoint #6 Primary Estimand	Change from baseline in muscle enzymes (creatine kinase [CK], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and aldolase) at Week 24	Difference in mean change from baseline in muscle enzymes (creatine kinase [CK], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and aldolase) at Week 24

- **Intercurrent events (ICEs) and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Composite Strategy:** Any value collected after experiencing the ICEs will be replaced by the baseline observation.
2. Discontinuation of study intervention for any reason, including COVID-19 infection but excluding other COVID-19 reasons	
3. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)	**Hypothetical Strategy:** This intercurrent event is addressed with a hypothetical strategy, as if the intercurrent event would not have occurred.

For subjects experiencing multiple ICEs simultaneously, ICEs in categories 1- 2 will override ICE 3.

5.3.3. Analysis Methods

Unless otherwise specified, the analysis population will be the all randomized analysis set defined in Section 2.3.2. P-values will be provided without adjusting multiplicity for secondary endpoints analyses.

Binary endpoint

Binary endpoint (secondary endpoint #2) will be based upon the primary estimand defined in Section 5.3.2, and will be analyzed using the same approach as the primary analysis for the primary endpoint: Logistic regression adjusting for 2 stratification factors (as per eCRF), disease subset (PM or DM) and baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]) as described in Section 5.2.3 will be used. Participants with ICEs 1-2 before Week 24 will be considered as experiencing disease worsening from the point of ICE forward. For participants with ICE 3, observed data will be used and no imputation will be applied.

Continuous endpoints

Continuous endpoints (secondary endpoints #1, 3, 4, 5, 6) will be based upon the primary estimands defined in Section 5.3.2 and will be analyzed using a Mixed Model Repeated Measures (MMRM) Model to test the difference between a ustekinumab group and placebo group and adjust for missing data. The models will include treatment, disease subset (PM or DM), baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent]) (as per eCRF), visit, and an interaction of treatment and visit as fixed effects. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, the compound symmetry structure will be used. The Kenward-Roger method will be used for approximating the denominator degrees of freedom.

The model will include all available data from two treatment groups through Week 24. The treatment difference between ustekinumab group and placebo group will be estimated by the difference in the least squares means (LSmeans). The 95% confidence interval (CI) for the differences in LSmeans and p-values will be calculated based on MMRM.

Residuals from the primary models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented to check whether there's any irregular trend of the residuals.

For participants who don't experience any ICEs, missing data will be imputed by baseline observation.

5.4. Other Efficacy Variable(s)

PM/DM Disease Activity

- The proportion of participants who achieve Minimal Improvement in IMACS TIS over time
- Mean change from baseline in PhGA of disease activity over time
- The proportion of participants with improvement in PhGA of disease activity over time
- Mean change from baseline in MMT-8 over time
- The proportion of participants with improvement in MMT-8 over time
- Mean change from baseline in Muscle enzymes (CK, ALT, AST, LDH, and aldolase) over time
- The proportion of participants with improvement in Muscle enzymes (CK, ALT, AST, LDH, and aldolase) over time
- Mean change from baseline in MDAAT over time
- The proportion of participants with improvement in MDAAT over time
- Mean change from baseline in FI-2 over time
- The proportion of participants who reduce the use of systemic glucocorticoid from baseline at Week 24
- The proportion of participants who reduce the use of systemic glucocorticoid from baseline and achieve Minimal Improvement in IMACS ITS at Week 24
- Time to worsening in participants who experience disease worsening through Week 24 based on consensus criteria for worsening
- The proportion of participants who achieve Moderate Improvement in IMACS TIS over time
- The proportion of participants who achieve Major Improvement in IMACS TIS over time
- IMACS TIS score over time

Patient-reported Outcomes

- Mean change from baseline in Patient Global Activity (PtGA) of disease activity at Week 24

- The proportion of participants with improvement in PtGA of disease activity at Week 24
- Mean change from baseline in Physical Function (Health Assessment Questionnaire Disability Index [HAQ-DI]) at Week 24
- The proportion of participants with improvement in Physical Function (HAQ-DI) at Week 24
- Mean change from baseline in 36-item short form (SF-36) including individual domains and component summary (PCS, MCS) scores at Week 24
- The proportion of participants with improvement in SF-36 including individual domains and component summary (PCS, MCS) scores at Week 24
- Mean change from baseline in PtGA of disease activity over time
- The proportion of participants with improvement in PtGA of disease activity over time
- Mean change from baseline in Physical Function (HAQ-DI) over time
- The proportion of participants with improvement in Physical Function (HAQ-DI) over time
- Mean change from baseline in SF-36 including individual domains and component summary (PCS, MCS) scores over time
- The proportion of participants with improvement in SF-36 including individual domains and component summary (PCS, MCS) scores over time

5.4.1. Definition

5.4.1.1. PM/DM Disease Activity Endpoints

See Section 5.2.1 for the definitions of related endpoints.

Minimal Improvement in IMACS TIS: Total improvement score of IMACS TIS ≥ 20

Improvement in PhGA of disease activity: Improvement score of PhGA of disease activity ≥ 7.5 or improvement based on absolute percentage change $> 5\%$

Improvement in MMT-8: Improvement score of MMT-8≥ 10 or improvement based on absolute percentage change $> 2\%$

Improvement in Muscle enzymes (CK, ALT, AST, LDH, and aldolase): For most abnormal enzyme at baseline, improvement score of enzyme ≥ 2.5 or improvement based on absolute percentage change $> 5\%$. The most abnormal enzyme is determined by having the greatest baseline value divided by its upper limit of normal.

Improvement in MDAAT: Improvement score of Extramuscular Assessment (MDAAT) ≥ 7.5 or improvement based on absolute percentage change $> 5\%$

Reduction of systemic glucocorticoid from baseline: The subject is considered as successful reduction if the latest nonmissing daily glucocorticoid dose before or on Study day 168 can be tapered as Table 8:

Table 8: Glucocorticoid Tapering Schedule (Daily Dose [mg] of Prednisolone or Equivalent)

Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
60	50	40	35	30	25	20	15	12.5
50	40	35	30	25	20	15	12.5	10
40	35	30	25	20	15	12.5	10	9
30	25	20	15	12.5	10	9	8	7
20	15	12.5	10	9	8	7	6	5
15	12.5	10	9	8	7	6	5	5
12.5	10	9	8	7	6	5	5	5
10	9	8	7	6	5	5	5	5

5.4.1.2. Patient-reported Outcomes Endpoints

See Section 5.2.1 for the definitions of Patient Global Activity-VAS and Functional Assessment (HAQ-DI).

Improvement in PtGA of disease activity: Improvement score of PtGA of disease activity ≥ 2.5 or improvement based on absolute percentage change $> 5\%$

Improvement in Physical Function (HAQ-DI): Improvement score of HAQ-DI ≥ 5 or improvement based on absolute percentage change $> 5\%$

36-item Short Form

The SF-36 consists of 8 subscales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. These subscales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Table 9: SF-36 subscales and items

Subscales	Items
Physical functioning	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role limitations due to physical health	4a, 4b, 4c, 4d
Role limitations due to emotional problems	5a, 5b, 5c
Energy/ fatigue	9a, 9e, 9g, 9i
Emotional well being	9b, 9c, 9d, 9f, 9h
Social functioning	6, 10
Pain	7, 8
General health	1, 11a, 11b, 11c, 11d

Improvement in SF-36: Improvement of 5 points in any of the subscales or 2.5 points of the component score

5.4.2. Analysis Methods

All other efficacy endpoints will be descriptively summarized by treatment groups. Treatment comparisons will be performed at Week 24. Nominal p values and 95% CI for the difference between ustekinumab group and placebo group will be provided. No treatment comparison will be performed after Week 24.

5.4.2.1. Analyses from Week 0 through Week 24

Binary Endpoints

The primary estimand approaches, and the corresponding analysis methods specified for the primary endpoint in Section 5.2.2, 5.2.3, will be applied to binary endpoints analysis at Week 24 as the main estimand.

For participants who experience intercurrent events before Week 24 as described in Section 5.3.2.1, the treatment policy strategy will be applied to binary endpoints that will be summarized over time through Week 24. The analysis will be performed based on observed data regardless of intercurrent events without imputation.

Continuous Endpoints

The primary estimand approaches, and the corresponding analysis methods specified for the secondary endpoint in Section 5.3.2.2, 5.3.3, will be applied to continuous endpoints analysis at Week 24 as the main estimand.

For participants who experience intercurrent events before Week 24 as described in Section 5.3.2.2, the treatment policy strategy will be applied to continuous endpoints that will be summarized over time through Week 24. The analysis will be performed based on observed data regardless of intercurrent events without imputation.

Time to Event Endpoint The following describes the attributes of the estimand for time to event endpoint.

- **Study intervention and Population:** Same attributes as primary estimand for primary endpoint
- **Variable/endpoint:** Time to event through Week 24, where the time to event is defined as time to disease worsening based on consensus criteria for worsening or time to any ICE in category 1 or 2.
- **Summary Measure (Population-level summary):** Hazard ratio of ustekinumab group and placebo
- **Intercurrent events (ICEs) and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. A prohibited change in PM/DM medications prior to Week 24	**Composite Strategy:** A participant with this intercurrent event is considered to experience disease worsening at the time of this event.
2. Discontinuation of study intervention for reasons: adverse event, death, prohibited medication or lack of efficacy	
3. Discontinuation of study intervention for remaining reasons	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this intercurrent event had occurred.

For subjects experiencing multiple ICEs simultaneously, ICEs in categories 1- 2 will override ICE 3.

For time to event endpoint, treatment comparison in time to worsening through Week 24 will be done using a log-rank test to report p-values. The hazard ratio and its associated 95% CI will be provided using the Cox proportional hazards model by adjusting for 2 stratification factors. The survival curves will be estimated using Kaplan-Meier estimates.

5.4.2.2. Analyses from Week 24 through Week 52/72/88

No imputation will be performed for missing data (eg, lost to follow up, missed study visit) and the values will remain as missing.

6. SAFETY

All safety analyses will be based on the safety analysis set as described in Section 2.3.3 above based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

The general definitions for analysis periods and treatment groups described in Section 2.4 and general data cut-off rules for Week 24/52/72 weeks described in Section 2.5 are applicable for safety analyses.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless

it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summary tables will be provided for treatment-emergent adverse events by defined analysis periods in Section 2.4 (from Week 0 through Week 24, from Week 24 through Week 52/72/88):

- TEAEs
- Serious TEAEs
- TEAEs leading to discontinuation of study agent/termination of study participation
- TEAEs by severity (mild, moderate, severe)
- TEAEs reasonably related to study agent
- Treatment emergent infections
- Treatment emergent infusion reactions
- Treatment emergent injection-site reactions
- Treatment emergent adverse events of special interest

A reasonably related AE is defined as any event with the relationship to study agent as 'very likely', 'probable', or 'possible' on the AE eCRF page or if the relationship to study agent is missing.

Opportunistic infection (ie, infection by an organism that normally is not pathogenic or does not cause invasive infection in immunocompetent hosts), case of active TB, ILD, or malignancy are considered as adverse events of special interest.

Summaries for above treatment-emergent adverse events from Week 0 to Week 52/72/88 will also be provided using patient-year method.

In addition to the summary tables, listings will be provided for subjects who:

- Had Serious TEAEs
- Had TEAEs leading to discontinuation of study agent/termination of study participation
- Any deaths

Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up for each treatment group.

6.2. Clinical Laboratory Tests

Descriptive statistics and graphical displays will be presented for selected chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points.

Change from baseline over time will be summarized for selected chemistry, hematology, and urinalysis (pH, and specific gravity) tests and displayed by treatment group.

- Hematology: Hemoglobin, Hematocrit, Red blood cell (RBC) count, White blood cell (WBC), Platelet count, Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils
- Chemistry: Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Total carbon dioxide (CO_2), Total bilirubin, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Total protein, Sodium, CK, Lactic acid dehydrogenase (LDH), Aldolase

A box plot of change from baseline over time will be provided for CK, LDH, Aldolase, ALT, AST

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.0) will be used in the summary of laboratory data (Grade 0-4). The proportion of subjects with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized by treatment group. Shift summaries from baseline laboratory value to the worst on-treatment grade in chemistry and hematology tests with NCI toxicity grades will be presented. Subjects with toxicity grades ≥ 2 will be listed.

For those labs without NCI toxicity grades, the incidence of markedly abnormal laboratory values will be presented by treatment group. Additionally, the markedly abnormal laboratory values will be listed. Markedly abnormal criteria are defined as Table 10:

Table 10: Markedly abnormal laboratory criteria

Item	Criterion of markedly abnormal criteria
Hematology & Differential panel	
Hemoglobin	$\leq 10 g/dL$
WBC	Out of normal range
Neutrophils	Out of normal range
Lymphocytes	Out of normal range
Chemistry panel	
ALT	$\geq 3 \times ULN$
AST	$\geq 3 \times ULN$
LDH	$\geq 3 \times ULN$
Creatinine	$\geq 1.5 \times ULN$
Glucose	$\geq 300 mg/dL$

Laboratory results from local lab will be excluded from summary analyses, but only included in the listings.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate, weight, pulse, blood pressure (systolic and diastolic) and SpO_2 will be summarized at each assessment time point. Change from baseline will be summarized by visit and treatment group. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of clinically important vital signs while on treatment, as defined in Table 11, will be summarized for subjects who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of subjects with clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Table 11: Clinically Important Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >15 bpm increase from baseline
	<50 bpm and with >15 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >20 mm Hg increase from baseline
	<90 mm Hg and with >20 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >15 mm Hg increase from baseline
	<50 mm Hg and with >15 mm Hg decrease from baseline
Temperature	>38°C
Respiratory rate	>24 breaths per minute
Weight	>10% kg increase from baseline
	>10% kg decrease from baseline
SpO_2	<90%

Vistal sign results from remote visits will be excluded from summary analyses, but only included in the listings.

6.4. Electrocardiogram

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of subjects meeting the normality criteria. The interpretation will be summarized over time by treatment group.

A listing of clinically relevant ECG abnormalities will also be provided.

6.5. Chest CT Scan and X-Ray

The interpretation of chest high-resolution CT scan and X-Ray will be summarized in number and percentage of subjects meeting the normality criteria over time by treatment group.

Listing of clinically relevant CT and X-Ray abnormalities will also be provided.

6.6. Pulmonary Function Test

Pulmonary function test (PFT) including vital capacity [VC], forced vital capacity [FVC], diffusing capacity of the lungs for carbon monoxide [DLCO], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and maximal voluntary ventilation [MVV] will be summarized at each assessment time point. Change from baseline will be summarized by visit and treatment group. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented. A listing of all pulmonary function test will be provided.

6.7. COVID-19 Summaries

Included in the adverse event summaries discussed in this section will be events related to COVID-19. These will be identified and coded using the MedDRA coding guidance for COVID-19. Summary tables may be provided for:

- COVID-19 related TEAEs

- Selected TEAEs of interest related to COVID-19
- Selected serious TEAEs of interest related to COVID-19

In addition to the summary tables, the following may be listed by subject:

- TEAEs related to COVID-19
- Serious TEAEs related to COVID-19
- Deaths related to COVID-19

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Blood samples will be collected to measure for serum ustekinumab concentration at the specified visits as shown in the Time and Events Schedule in protocol. PK analyses will be performed on the PK analysis set (see Section 2.3.4) and summarized from Week 0 to Week 24/52/72/88 for Week 24 DBL, Week 52 DBL, Week 72 DBL and Week 88 DBL respectively.

Serum ustekinumab concentrations summary will be based on the observed data; therefore, no imputation for missing concentration data will be performed. All participants and samples excluded from the analysis will be clearly documented (eg, unknown or unreliable drug intake information).

All PK data including actual sampling time will be listed. All serum ustekinumab concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset.

Descriptive statistics (N, mean, SD, median, range, CV (%), geometric mean and IQ range) will be used to summarize serum ustekinumab concentrations by intervention group (ustekinumab or placebo- >ustekinumab) at each sampling time point.

For descriptive statistics of serum ustekinumab concentrations, the following data handling rules will be applied;

- Participants will be excluded from the descriptive statistics if their data do not allow for accurate assessment of the PK. In particular, all serum concentration data will be excluded, from the time of occurrence, data collected for participants who 1) discontinue ustekinumab, 2) skip an infusion or injection, 3) receive an incomplete infusion or injection, 4) receive an incorrect infusion or injection, 5) receive an additional infusion or injection, and/or 6) receive commercial ustekinumab. Exclusion data from the descriptive statistics due to such inadequate administration will be specified by PK analyst. In addition, PK samples taken outside the scheduled visit window (**±7 days**) will be excluded from the descriptive statistics.
- Data of each concentration with no information about the sampling date and time and/or the drug administration (time and dosage) will be excluded from descriptive statistics.
- Serum ustekinumab concentrations below the LLOQ will be imputed as zero in the summary statistics.

- When more than half (>50%) of the serum concentrations of ustekinumab are below quantification limit (BQL) at each scheduled time point, mean, median and minimum will be shown as 'BQL', and SD and %CV will be shown as 'NC' (not calculated). IQ range [minimum (25% quartile) and maximum (75% quartile)] will be shown as 'BQL-NC'. Maximum observed value will be presented as maximum.
- When all serum concentration data are BQL at each scheduled time point, mean and median will be reported as 'BQL'; SD and %CV are reported as 'NC' (not calculated); IQ range, maximum and minimum will be reported as 'BQL'.
- When the number of serum concentrations data of ustekinumab at each scheduled time point is less than or equal to 2, N, mean and median will be calculated, and SD and %CV will be shown as 'NC'. IQ range [minimum (25% quartile) and maximum (75% quartile)] will be shown as 'NC-NC'. Minimum and maximum will be shown as 'NC' (number of quantifiable data=1) or will be reported as observed including BQL (number of quantifiable data =2).
- At the time point where no observation is obtained, 'NA (not applicable)' is reported.
- Sampling time at Week 0 pre-dose will be substituted with "0". The data point which means of serum ustekinumab concentration is BQL will be treated as LLOQ value (eg, 0.16880 µg/mL) in graph.

Analysis period

See Section 2.4.

Table

From Week 0 through Week 24, serum ustekinumab concentration in ustekinumab arm will be summarized in table. From Week 24 through each timepoint (Week 52/72/88), serum ustekinumab concentration in all participants will be summarized in table by intervention group (ustekinumab or placebo- >ustekinumab). In addition, to assess the impact of weight-based IV dosing (~6 mg/kg), serum ustekinumab concentrations from Week 0 to Week 8 in ustekinumab group and from Week 24 to Week 32 in placebo->ustekinumab group will be summarized in a separate table by weight-based dose category (See Section 1.2). To assess the impact of body weight on maintenance therapy (90 mg SC q8w), serum ustekinumab concentrations from Week 0 through each timepoint (Week 24/52/72/88) in ustekinumab group by body weight quartile will summarized.

Figure

Serum ustekinumab concentrations data may be displayed graphically, such as median (±inter quartile range, IQR) of serum ustekinumab concentrations over time by intervention group by the following subgroups:

- Median (±IQR) of serum ustekinumab concentration time profiles through Week 24 (in linear and semi-log scales) with nominal sampling time will be presented in figure.
- Median (±IQR) of serum ustekinumab concentration time profiles through each timepoints (Week 52/72/88) (in linear and semi-log scales) with nominal sampling time will be presented in figure.

Listing

The elapsed time[day] from last dosing to next PK sampling point will be described in listing.

Other

If sufficient data are available, then population PK analysis using serum concentration-time data of ustekinumab will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

7.2. Immunogenicity Analyses

Blood samples will be collected for the detection of antibodies to ustekinumab at the specified visits as shown in the Time and Events Schedule in protocol. Immunogenicity analyses will be based on the immunogenicity analysis set (see Section 2.3.5) and summarized from Week 0 to Week 24/52/72/88 for Week 24 DBL, Week 52 DBL, Week 72 DBL and Week 88 DBL respectively.

"Sample ADA status" and sample titer as well as the cumulative "subject ADA status" and peak titer through the visit will be coded and provided by the bioanalytical group.

"Subject ADA status" is defined as below.

- Participants with treatment-emergent ADA positive to ustekinumab include
  - Participants with treatment-induced antibodies to ustekinumab
  - Participants with treatment-boosted antibodies to ustekinumab
- Participants with treatment-induced antibodies to ustekinumab have a negative sample prior to administration and at least one positive sample after administration
- Participants with treatment-boosted antibodies to ustekinumab have a positive sample prior to administration and at least one positive sample after administration with increase in titer over baseline

Incidence of antibody status (Subject with baseline positive samples, treatment-emergent ADA positive to ustekinumab, treatment-emergent ADA negative to ustekinumab), the maximum titers of anti-ustekinumab antibodies and incidence of Neutralizing antibodies (NAb) from Week 0 through each timepoint (Week 24/52/72/88) will be summarized by intervention groups.

The summary of following endpoints (ustekinumab concentration, the proportion of participants who achieve IMACS TIS minimal improvement at Week 24, and injection site reactions status) will be presented by intervention group by treatment-emergent antibodies to ustekinumab status (positive or negative).

1. Descriptive statistics (N, mean, SD, median, range, and IQ range) and incidence (N, %) of the relationship between treatment-emergent antibodies to ustekinumab status (positive or negative) and ustekinumab concentration from Week 0 through each timepoint (Week 24/52/72/88)

2. Participants in response (N, %) for treatment-emergent antibodies to ustekinumab status (positive or negative) and efficacy endpoints (The proportion of participants who achieve IMACS TIS minimal improvement at Week 24)
3. Incidence (N, %) between treatment-emergent antibodies to ustekinumab status (positive or negative) and injection site reactions status from Week 0 through each timepoint (Week 24/52/72/88)

7.3. Pharmacokinetic/Pharmacodynamic Relationships

If data permit, the relationship between serum ustekinumab concentration (PK data) and efficacy measures for primary and selected key secondary endpoints (PD data) may be analyzed tabularly or graphically (PK/PD analysis). PK/PD analysis will be performed on the PK/PD analysis set (see Section 2.3.7), defined as below: all subjects (including participants who received placebo intervention) who have at least 1 paired PK and PD data collected at same time point needed for each PK/PD analysis. If participants who receive placebo intervention and have no concentration data, serum ustekinumab concentrations will be imputed as zero.

Following PD data will be used in PK/PD analysis: International Myositis Assessment and Clinical Studies Total Improvement Score (IMACS TIS) minimal improvement, IMACS TIS, Manual Muscle Testing (MMT)-8, Extramuscular Assessment (Myositis Disease Activity Assessment Tool [MDAAT]-Extramuscular Global Assessment), creatinine kinase (CK).

The data of IMACS TIS response used for PK/PD analysis will be imputed following data handling rules for primary estimand of primary efficacy endpoint. Plots for IMACS TIS, MMT-8, MDAAT, CK would be based on observed data without imputation.

IMACS TIS minimal improvement

Serum ustekinumab concentrations (N, median, range [min-max]) at Week 24 will be tabulated by responder status (achieved/not-achieved IMACS TIS minimal improvement). For this analysis the subjects randomized to Placebo group at Week 0 will be excluded from PK/PD analysis set.

In addition, the proportion of participants who are randomized to ustekinumab intervention group and achieve IMACS TIS minimal improvement at Week 24 will also be tabulated by ustekinumab concentration categories (placebo, <= median or >median).

IMACS TIS

Relationship between individual total improvement score in IMACS TIS and serum ustekinumab concentrations at Week 24/48 will be summarized using box plot by intervention groups (for Week 24: ustekinumab and placebo, for Week 48: ustekinumab and placebo -> ustekinumab) and by ustekinumab concentration categories (<= median or >median). Individual values will be plotted over the box plot on the same figure.

MMT-8

Relationship between individual change from baseline in MMT-8 and serum ustekinumab concentrations at Week 24/48 will be summarized using box plot by intervention groups

(ustekinumab and placebo -> ustekinumab) and by ustekinumab concentration categories (<= median or >median). The graph at Week 48 will be shown separately by intervention group (ustekinumab or placebo- >ustekinumab). Individual values change from baseline will be plotted over the box plot on the same figure.

MDAAT

Relationship between individual change from baseline in MDAAT and serum ustekinumab concentrations at Week 24/48 will be summarized using box plot by intervention groups (ustekinumab and placebo -> ustekinumab) and by ustekinumab concentration categories (<= median or >median). The graph at Week 48 will be shown separately by intervention groups (ustekinumab or placebo- >ustekinumab). Individual values change from baseline will be plotted over the box plot on the same figure.

CK

Relationship between individual percentage change from baseline in CK at Week 24/48 and serum ustekinumab concentrations at Week 24/48 will be plotted in scatter plot. Data collected from both ustekinumab and placebo group will be used and plotted on the same graph with different symbols.

In addition to the above-mentioned assessments, population PK/PD analysis may also be performed using nonlinear mixed-effects modeling. Details will be given in a population PK/PD analysis plan and the results of the analysis will be presented in a separate report.

8. BIOMARKERS

Biomarker results will be summarized in a separate technical report. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

Genetic (DNA) analyses will be conducted only in participants who sign the optional DNA consent form. These analyses will be summarized in a separate technical report.

9. REFERENCES

Aggarwal R., Rider LG., Ruperto N., Bayat N., Erman B., Feldman BM., et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: An International Trials Organisation Collaborative Initiative. Ann Rheum Dis. 2017. 76(5): 792-801.

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ATTACHMENTS

Appendix 1 Prohibited Changes in PM/DM Medications Prior to Week 24

Only applied during the double-blind portion of the study (from Week 0 through Week 24).

- There was addition of a new immunomodulator to the existing treatment regimen
  - Initiation of a new immunomodulator indicated to treat PM/DM to the existing treatment (i.e. present at randomization) during the double blind period and this immunomodulator does not completely replace the existing immunomodulator of similar mechanism of action (i.e. MMF or AZA or Oral MTX or Oral TAC or Oral cyclosporine A)
- The dose of an immunomodulator is higher than at baseline
  - Exceeding the 110% of baseline dose of the existing treatment (i.e. present at randomization) in daily dose for any week (Week 1 ~ Week 24) during the double-blind period. Baseline immunomodulator dose is defined as the daily dose on Study day -1 (the day before randomization). The daily dose for Week n (an integer from 1 to 24) is defined as the latest non-missing daily dose on Study day 7*n-6 to 7*n. For example, the daily dose for Week 2 will be the dose taken on Study day 14, if Study day 14 dose is not missing.
- For the patients with baseline glucocorticoids dose=0, initiation of sustained treatment with oral or IV glucocorticoids for PM/DM-related disease activity, Baseline glucocorticoids dose is defined as the daily dose on Study day -1 (the day before randomization).
  - I Initiation of oral glucocorticoids indicated to treat PM/DM and sustained for at least 7 consecutive days during the double-blind period.
  - Receiving any IV (including intravenous drip) glucocorticoids indicated to treat PM/DM during the double-blind period.
- For the patients with baseline glucocorticoids dose > 0, the dose of oral glucocorticoids is higher than baseline dose, increased dose below the baseline dose more than once, or remains stable dose without glucocorticoid tapering schedule (see Table 2 in section 6.5.2 of the protocol) for consecutive 6 weeks or longer during the period from Week 2 through Week 16. The switching to glucocorticoid with equivalent potency is not considered a prohibited change. Baseline glucocorticoids dose is defined as the daily dose on Study day -1 (the day before randomization).
  - Exceeding the 110% baseline dose in daily dose for any 2-weeks (Week 0 ~ Week 2, Week 2~Week4, …Week 22~Week 24) period during the double period.
  - Receiving any IV (including intravenous drip) glucocorticoids indicated to treat PM/DM during the double-blind period.
  - During the period from Week 2 through Week 16, continue a daily glucocorticoid dose > 5mg for consecutive >= 3 times i.e., continue a daily glucocorticoid dose > 5mg for >=4 consecutive 2-weeks.
  - During the period from Week 2 through Week 16, continue a daily glucocorticoid dose > 5mg for consecutive >= 2 times more than once, i.e., continue a daily glucocorticoid dose > 5mg for >=3 consecutive 2-weeks more than once.

- 2-weeks daily dose exceeds the previous one more than once during the period.

The daily dose for Week n (a multiple of 2 from 2 to 24) is defined as the latest non-missing daily dose on Study day 14*n-13 to 14*n. For example, the daily dose for Week 8 will be the dose taken on Study day 56, if Study day 56 dose is not missing; otherwise, it will be the dose taken on Study day 55, if Study day 55 dose is not missing.

Subjects who have a prohibited change in PM/DM medications and reason the change will be listed.

Appendix 2 Unblinding Plan

Primary endpoint of this study will be evaluated at Week 24. Long-term safety and efficacy of ustekinumab will continue being evaluated after Week 24. Investigative study sites and participants will remain blinded to treatment assignment until the DBL at Week 52. At the Week 24 DBL, the data will be unblinded to sponsor for analysis while participants are still participating in the study. At Week 24 DBL, a document containing the Week 24 topline results (TLR) will be developed and distributed as per sponsor SOP-05501 (Preparation and Communication of Topline Results). Furthermore, these topline results will support sponsor's decision on whether applying for orphan designation.

During the period from Week 24 DBL until Week 52 DBL of this study, in order to maintain the blindness of subjects and investigators to protect the trial integrity and minimize the potential influence on the behavior of the subjects and investigators who still participate this trial, access to the unblinded data [a] will be protected as defined in this unblinding plan. In principle, the sponsor unblinders will be limited to the sponsor personnel who are involved in activities on orphan drug application and are notified not to disclose any data to any non-unblinders. In principle, medical monitors from sponsor or Contract Research Organization (CRO) will continue to be blinded to all data until Week 52 DBL. The sponsor unblinders in each group are as follows:

1. JCoT (Japan Compound Team)

JCoT is a sponsor organization that is responsible for developing PM/DM indication for ustekinumab in Japan.

2. TLR-related personnel

The TLR results will be prepared and communicated as per sponsor SOP-05501. Therefore, all the TLR reviewers/approvers and the personnel who are pre-defined in the TLR distribution list will be unblinded.

3. Data management and analysis personnel

These members will be unblinded to clean/analyze the data.

4. Other orphan drug application documents writers/reviewers/supporters

Upon JCoT members' judgment, sponsor personnel other than JCoT members who need to access to the unblinded data to write/review/support orphan drug application documents can also be the unblinders.

[a] The unblinded data includes the data unblinded to individual subject treatment assignments, e.g., statistical listings and subject narratives and study results by the treatment group without disclosing the individual treatment assignments, e.g., statistical tables/figures.

The sponsor study statistician will keep a running log of personnel who have been unblinded to the data and the date of unblinding during the implementation period of this unblinding plan (from Week 24 DBL until Week 52 DBL).

Any sponsor personnel other than the above unblinders will not have access to the unblinded data. All the unblinded data will be kept appropriately in a sponsor Sharepoint accessible to unblinders only. Before sharing the unblinded data with any new unblinders, it should be clearly noted that "it's an ongoing study and all the study results disclosed are required to be confidential from the investigators and subjects of this study.". When distributing the topline results (TLR), the note of "Confidential and forwarding is strictly prohibited." should be included to avoid further dissemination.