Janssen Pharmaceutical K.K.*

Clinical Protocol

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
AMENDMENT 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. The sponsor is identified on the Protocol Supplementary Information, which will be provided as a separate document.

Status: Approved
Date: 29 November 2021
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-ERI-173744989, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	29 November 2021
Amendment 2	4 June 2020
Amendment 1	13 Aug 2019
Original Protocol	13 Feb 2019

Amendment 3 (30 Nov 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to align with internal standard on study estimands based on the latest considerations on statistical analyses.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis Tertiary Endpoints, *PM/DM Disease Activity* 3. OBJECTIVES AND ENDPOINTS Tertiary Endpoints, *PM/DM Disease Activity*	Added text on tertiary endpoints of PM/DM disease activity.	Text was revised to clarify tertiary endpoints of PM/DM disease activity.
1.1 Synopsis OVERALL DESIGN 4.1. Overall Design 6.3. Measures to Minimize Bias: Randomization and Blinding, Blinding	Updated and added text on unblinding timing.	Text was revised to change the unblinding timing.
1.1 Synopsis Primary Efficacy Analysis 7.1. Discontinuation of Study Drug 9.4.1.1. Primary Endpoint Analysis 9.4.1.1.1. Primary Estimand	Added intercurrent events (ICEs) to the study estimands, rephrased the primary estimand sections, and deleted treatment failure.	To align with internal standard, text was revised to clarify the study estimands, introduce the ICE to the study estimands and re-phrase the primary estimand sections. Meanwhile, incorporate the treatment failure rules into the ICE handling rules.
1.1 Synopsis Secondary Efficacy Analyses 9.4.1.2. Secondary Efficacy Analyses	Added strategies to address the ICEs for secondary efficacy.	Text was added to clarify strategies to address the ICEs for secondary efficacy analyses.
9.4.1.1. Primary Endpoint Analysis	Updated text on missing data.	Text was revised to address the ICEs.
9.4.1.1.2. Estimands other than the primary estimand	Updated text on sensitivity/supplemental analyses.	Text was revised to add supplemental estimand.
9.4.2. Safety Analyses Adverse Events	Added text on AEs of COVID-19.	Text was added to capture AEs of COVID-19 during the COVID-19 pandemic.
Throughout the protocol	Minor grammatical formatting or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

STELARA® (ustekinumab) is a fully human G1 kappa monoclonal antibody that binds with high affinity and specificity to the shared p40 subunit of human interleukin (IL)-12 and IL-23 cytokines. The binding of ustekinumab to the IL-12/23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer and cluster of differentiation (CD)4+ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including polymyositis (PM)/dermatomyositis (DM). Therefore, inhibition of IL-12 and IL-23 has the potential to be effective in the treatment of PM/DM.

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

The primary objective is 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).

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

Endpoints

Primary Endpoint

The primary endpoint is the proportion of participants who achieve Minimal Improvement in International Myositis Assessment and Clinical Studies Total Improvement Score (IMACS TIS) at Week 24.

Secondary Endpoints

The secondary endpoints are:

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

Tertiary Endpoints

PM/DM Disease Activity

- The proportion of participants who achieve Minimal Improvement in IMACS TIS over time
- 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
- Mean change from baseline in PhGA over time
- The proportion of participants with improvement in PhGA 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

Patient-reported Outcomes

- Mean change from baseline in Patient Global Activity (PtGA) at Week 24
- The proportion of participants with improvement in PtGA 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 over time
- The proportion of participants with improvement in PtGA 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

Pharmacokinetics and Immunogenicity

- Summary of serum ustekinumab concentrations
- Incidence of anti-ustekinumab antibodies

Biomarkers

- Biomarkers of ustekinumab treatment response over time

Hypothesis

Treatment with ustekinumab is superior to placebo in participants with active PM/DM despite receiving 1 or more standard-of-care treatments as measured by the proportion of participants achieving IMACS TIS at Week 24.

OVERALL 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.

Approximately 50 participants will be randomly assigned in a 1:1 ratio to receive either ustekinumab or matching placebo with the following treatment administrations:

- Week 0: Body weight-range based intravenous (IV) administration of ustekinumab (~6 mg/kg) or placebo
- Week 8 and Week 16: subcutaneous (SC) administration of 90 mg ustekinumab or placebo

- Week 24: Placebo group participants crossover to receive body weight-range based IV administration of ustekinumab (~6 mg/kg) and placebo SC and ustekinumab group participants receive placebo IV and continue with SC administration of 90 mg ustekinumab
- Week 32, Week 40, Week 48, Week 56, Week 64, and Week 72: SC administration of 90 mg ustekinumab

A placebo comparator (in addition to standard-of-care background therapy) will be used in this study through Week 24 to allow for blinded, placebo-controlled evaluation of the efficacy and safety of ustekinumab in participants with PM/DM.

Randomization 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]) using permuted block central randomization.

Four database locks (DBLs) will occur 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. Investigative study sites and participants will remain blinded to initial treatment assignment until the DBL at Week 52. After the Week 24 DBL, the data will be unblinded to sponsor for analysis while 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. 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.

An external independent data monitoring committee (IDMC) will be commissioned for this study.

A futility analysis will be carried out after 20 participants complete Week 24 visit. The analysis will be performed in an unblinded fashion by the IDMC based primarily on Week 24 efficacy data. The details of the futility analysis will be included in the interim analysis plan.

The end of study is considered as the last follow-up assessment at Week 88 for the last participant in the study.

NUMBER OF PARTICIPANTS

Approximately 50 participants are planned to be enrolled in the study.

INTERVENTION GROUPS AND DURATION

Following randomization at Week 0, participants assigned to the active treatment group will receive an initial body weight-range based IV dose ~6 mg/kg of ustekinumab (ustekinumab 260 mg weight ≤55 kg; ustekinumab 390 mg weight >55 kg and ≤85 kg; ustekinumab 520 mg weight >85 kg), and participants who were randomized to placebo will receive a single IV dose of placebo. Starting at Week 8, participants will receive SC dosing with either placebo or ustekinumab 90 mg q8w through Week 24. At Week 24, participants receiving placebo will crossover to receive body weight-range based IV administration of ustekinumab. Starting at Week 32, all participants will receive ustekinumab 90 mg SC q8w through Week 72.

Week 0 up to Week 16

Group 1: Participants will receive body weight-range based IV dosing of ~6 mg/kg of ustekinumab at Week 0 followed by ustekinumab 90 mg SC administrations at Weeks 8 and 16.

Group 2: Participants will receive IV dosing of placebo at Week 0 followed by placebo SC administrations at Weeks 8 and 16.

Week 24

Group 1: Participants will receive IV dosing of placebo and ustekinumab 90 mg SC administration.

Group 2: Participants will receive body weight-range based IV dosing of ~6 mg/kg of ustekinumab and placebo SC administration.

Week 32 up to Week 72

Groups 1 and 2: Participants will receive ustekinumab 90 mg SC q8w administrations through Week 72.

EFFICACY EVALUATIONS

Measures of global disease activity: PhGA and PtGA for global evaluation of the patient's overall disease activity at the time of assessment using a 10 cm Visual Analogue Scale (VAS).

Measures of muscle: Manual Muscle Testing (MMT) to assess muscle strength, muscle enzymes to measure the serum activities of muscle-associated enzymes including CK, the transaminases (ALT, AST), LDH, and aldolase, MDAAT to measure the degree of disease activity of extramuscular organ systems and muscle, and FI-2 for assessing muscle endurance in participants with PM/DM.

Patient-reported outcomes (PROs): Health Assessment Questionnaire Disability Index (HAQ-DI) for physical function and SF-36 survey to assess generic health-related quality of life (HRQOL).

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

- Summary of serum ustekinumab concentrations and presence of anti-ustekinumab antibodies
- Pharmacokinetics (PK)-efficacy relationships for primary and selected key secondary endpoints
- If data allow, population PK and population PK-pharmacodynamics (PD) analysis on primary and/or selected key secondary efficacy endpoints

PHARMACOGENOMIC EVALUATIONS

A pharmacogenomic blood (whole blood deoxyribonucleic acid [DNA]) will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

BIOMARKER EVALUATIONS

Assessments will be performed to identify biomarkers that are relevant to ustekinumab treatment. These may include but not limited to, immune, inflammatory and other soluble protein markers, gene expression markers in ribonucleic acid (RNA), phenotypic and functional cellular markers and, for patients who complete the optional DNA informed consent, DNA markers related to susceptibility and polymorphisms.

- Ig isotype profile (IgG, IgM, IgA levels)
- IL-12/IL-17/IL-23 (eg, messenger RNA [mRNA], Soluble Protein [Serum])
- Anti-aminoacyl-transfer RNA (tRNA) synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS)
- Anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR
- Type I, II, and III interferons (IFNs)
- Other inflammation-related molecules and autoantibody profile

SAFETY EVALUATIONS

Safety evaluations will include assessment of adverse event (AEs), concomitant medications, pregnancy testing, administration reactions, serum chemistry, hematology and blood coagulation laboratory tests, vital signs, ECG, general physical examinations, and TB testing. In addition, HIV, hepatitis B, and hepatitis C, will be required at screening. The presence of interstitial lung disease (ILD) and respiratory muscle weakness will be evaluated using x-ray, chest high-resolution computer tomography (HRCT), blood gas analysis (partial pressure of oxygen in arterial blood [PaO_2] and partial pressure of carbon dioxide in arterial blood [$PaCO_2$]), and pulmonary function test (PFT) (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]). All participants must be monitored with SpO_2 and laboratory data (KL-6 and SP-D) regularly during the study.

STATISTICAL METHODS

Simple descriptive summary statistics, such as sample size (n), mean, standard deviation (SD), median, interquartile (IQ) range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

In general, all statistical tests will be performed at a 2-sided significance level of α=0.05.

Sample Size Determination

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).

Efficacy Analysis

It is considered that the effectiveness of ustekinumab treatment in adult patients with PM/DM will be demonstrated if the ustekinumab group is shown to be superior to placebo group for the primary efficacy analysis in this study.

Primary Efficacy Analysis

The primary endpoint of this study is the proportion of participants who achieve IMACS TIS response at Week 24. 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. 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.
- **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.

Logistic regression adjusting for 2 stratification factors, 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 between the ustekinumab and placebo groups and the 95% confidence interval will be provided.

Secondary Efficacy Analyses

All endpoints other than the primary endpoint of this study are not prospectively powered and all p-values reported for the secondary endpoints will be considered nominal.

- Treatment comparison in time to worsening through Week 24 will be done using a log-rank test. Kaplan-Meier estimates will be provided for each treatment group. Analysis for time to worsening will be repeated adjusting for 2 stratification factors using a proportional hazards model. In the analyses for time-to-event endpoints, subjects with ICE 1-2 will be handled with **Composite Strategy** and subjects with ICE 3 will be handled with **Treatment Policy Strategy** (the observed data will be used regardless of whether or not this ICE had occurred)**.**
- Analyses comparing the 2 treatment arms will be performed using a logistic model similar to primary analysis with the binary outcome related to individual core set measures at Week 24. The primary estimand approaches dealing with ICEs will be applied to these analyses.
- All other efficacy endpoints will be summarized over time by treatment group. Treatment comparisons will be performed using a mixed-effect model repeated measure (MMRM) model where there are repeated continuous measurements or a logistic model where there is a dichotomous response variable. The primary estimand approaches dealing with ICEs will be applied to these analyses also and the detailed methods of analysis and the data-handling rules will be provided in the statistical analysis plan (SAP).

Safety Analyses

All safety analyses will be based on the population of participants who receive at least 1 dose of either study drug; participants will be summarized by the treatment they receive. Adverse events, serious adverse event

(SAEs), reasonably related AEs, and AEs by severity will be summarized by treatment group. More specification of other special interesting event such as malignancies, serious infections, serious cardiovascular events and ILD will be described in the SAP. However, a summary table will not be provided if the number of events is too few to provide meaningful summary. The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of participants with abnormal laboratory parameters (hematology and chemistry) based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) toxicity grading will be summarized by treatment group. Listings of SAEs will also be provided.

Other Analyses

Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized over time. Descriptive statistics, including arithmetic mean, SD, median, IQ range, minimum, and maximum will be calculated at each sampling time point. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

If feasible, population PK analysis of ustekinumab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Biomarkers Analyses

Biomarker analyses performed may include but not limited to serum analysis for levels of IFNs as well as molecular pathway profiling for evidence of IL-12 and IL-23 pathway modulation. The biomarkers analyzed may include inflammatory markers, RNA, autoantibodies, T, B, and natural killer (NK) cell immunophenotyping, and other categories of biomarkers potentially involved in the development and the progression of PM/DM.

Biomarker results will be summarized in a separate technical report.

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.

Immunogenicity Analyses

The incidence of anti-ustekinumab antibodies and the impact of antibodies on serum ustekinumab concentrations will be summarized for all participants who receive at least 1 dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 sample obtained after their first dose of ustekinumab). The incidence of neutralizing antibodies (NAbs) to ustekinumab will be summarized for participants who are positive for antibodies to ustekinumab and have samples evaluable for NAbs to ustekinumab.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum ustekinumab concentration and efficacy measures for primary and selected key secondary endpoints will be analyzed graphically. In addition, population PK/PD modeling may be performed to characterize the relationship between serum ustekinumab exposure and efficacy measures. Further details will be provided in a population PK/PD analysis plan and the results will be provided in a separate report.

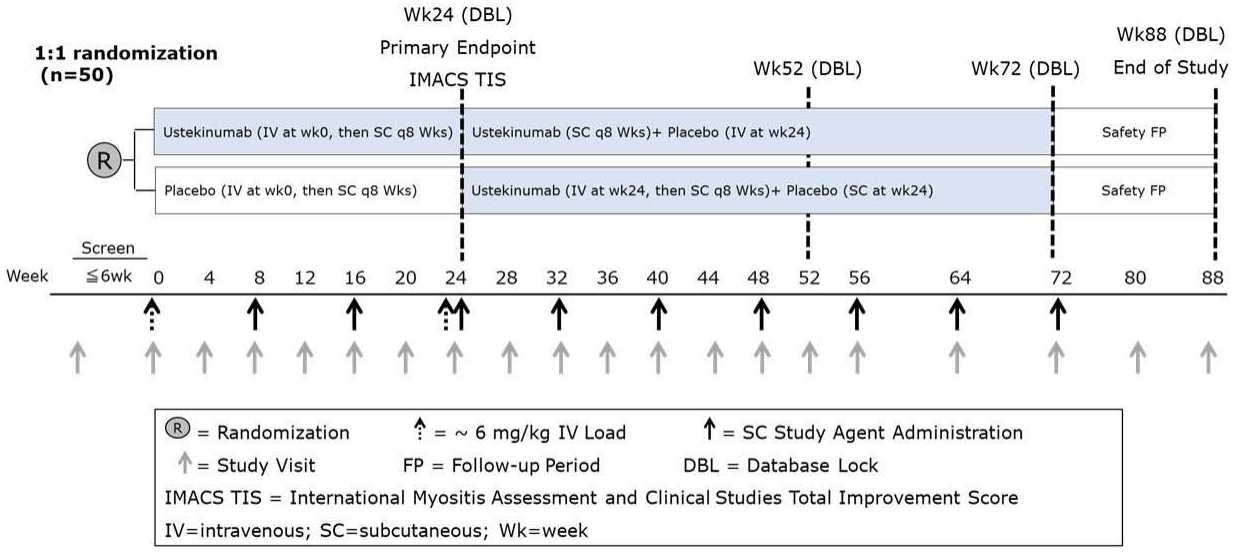
Interim Analysis

A futility analysis based on the primary endpoint of IMACS TIS at Week 24 will be conducted when 20 participants (40% of the originally planned total sample size) have completed the Week 24 visit. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) is less than a prespecified cutoff. The prespecified cutoff value will be 0.20. For the futility analysis, the treatment assignment information will be unblinded to IDMC and independent statistical support group for the 20 participants included in the interim analysis only (the treatment assignment for the remaining participants will remain blinded at this time). The details will be stated in interim analysis charter.

The simulation study demonstrates that this futility analysis will result in a slight loss in power (≤0.6%) when the treatment effect is expected to be 40% assuming the response rate in the placebo group as 25% and Type I error rate will not inflate (α=0.05, 2-sided) for the primary endpoint analysis.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

TIME AND EVENTS SCHEDULE - Screening Through 8-weeks/16-weeks Follow-up																				
	Screening[a]	Double-blind period							Cross-over administration period										Follow-up	
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**64**	**72**	**80 or EO-Treatment[b]**	**88 *or* EO-Trial[c]**
Acceptable deviation (days)		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Study Procedures[d]																				
Screening/Administrative																				
Informed consent[e]	X																			
Inclusion/exclusion criteria[f]	X	X																		
PM/DM classification by EULAR/ACR classification criteria	X																			
Myositis Damage Index -VAS (Muscle Damage)	X																			
Medical history and demographics	X																			
Study drug Administration[g]																				
Randomization		X																		
Study drug administration at study site		X		X		X		X		X		X		X		X	X	X		
Issue participant diary cards	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant diary cards returned to clinic		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																				
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
ECG[h]	X							X											X	
ILD and respiratory muscle evaluation[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray (both posterior-anterior and lateral views)[j]	X[k]	X			X			X			X			X			X		X	X
Chest HRCT	X[l]				X			X						X					X	
Blood gas analysis (PaO_2 and $PaCO_2$)	X																			

TIME AND EVENTS SCHEDULE - Screening Through 8-weeks/16-weeks Follow-up																				
	Screening[a]	**Double-blind period**							**Cross-over administration period**										**Follow-up**	
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**64**	**72**	**80 or EO-Treatment[b]**	**88 *or* EO-Trial[c]**
Acceptable deviation (days)		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Pulmonary function test (VC, FVC, DLCO, MIP and MEP and/or MVV)	X				X			X			X			X			X		X	
KL-6, SP-D	X	X	X	X	X	X	X	X		X		X		X		X	X	X	X	X
SpO_2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGRAs (T-SPOT.TB test or QFT)	X																			
HIV, HBV, and HCV screening	X																			
Urine pregnancy test[n]	X	X		X		X		X		X		X		X		X	X	X	X	X
Infusion or injection-site reaction evaluation[o]		X		X		X		X		X		X		X		X	X	X		
Review concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glucocorticoid tapering[p]		← Weeks 2 to 16 →							← Weeks 24 to 80 →											
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																				
ClinROs[q]																				
Physician Global Activity (PhGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MMT[r]	X	X	X	X	X	X	X	X		X		X		X			X		X	
MDAAT	X	X	X	X	X	X	X	X		X		X		X			X		X	
FI-2	X	X	X	X	X	X	X	X		X		X		X			X		X	
PROs[s]																				
Patient Global Activity (PtGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	X	X	X		X		X		X			X		X	
SF-36		X						X						X					X	
FI-2 (Muscle exertion Borg CR-10)[t]	X	X	X	X	X	X	X	X		X		X		X			X		X	

TIME AND EVENTS SCHEDULE - Screening Through 8-weeks/16-weeks Follow-up																				
	Screening[a]	Double-blind period							Cross-over administration period										Follow-up	
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**64**	**72**	**80 or EO-Treatment[b]**	**88 *or* EO-Trial[c]**
Acceptable deviation (days)		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Clinical Laboratory Assessments[u]																				
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X																			
Urine Analyses (spot urine)[u]																				
Urinalysis (dipstick, all participants)	X	X		X		X		X		X		X		X		X	X	X	X	X
Urine sediment analysis	X																			
PK/ Immunogenicity[v]																				
Serum ustekinumab concentrations[v]		2X[w]	X	X	X	X	X	X		X		X		X		X	X	X	X	X
Population PK[x]		← X → (Weeks 0 to 8)			← X → (Weeks 12 to 20)															
Antibodies to study drug		X	X		X			X				X		X					X	
Biomarkers[v]																				
Autoantibody profiling	X							X												
Ig isotype profile	X	X	X		X			X				X		X			X		X	
Serum biomarkers	X	X	X		X			X				X		X			X		X	
PBMC (immunophenotyping and functional analysis)[y]	X	X	X		X			X				X		X			X		X	
Whole blood (RNA)	X	X	X		X			X				X		X			X		X	
Whole blood (DNA)[z]	X																			

Key: ACR=American College of Rheumatology; ClinROs=Clinician Reported Outcomes DLCO=diffusing capacity of the lungs for carbon monoxide; DM=dermatomyositis; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EO=end-of; EULAR=European League Against Rheumatism; FI-2=Functional Index-2; FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire Disability Index; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRCT=high-resolution computer tomography; Ig=immunoglobulin; IGRAs=interferon gamma release assays; ILD=interstitial lung disease; MDAAT=Myositis Disease Activity Assessment Tool; MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure; MMT=Manual Muscle Testing; RNA=ribonucleic acid; MVV=maximal voluntary ventilation; $PaCO_2$=partial pressure of carbon dioxide in arterial blood; PaO_2=partial pressure of oxygen in arterial blood; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; PM=polymyositis; PRO=patient-reported outcomes; QFT=QuantiFERON-TB Gold; SF-36=36-item short form; TB=tuberculosis; VAS=Visual Analogue Scale; VC=vital capacity.

a. Screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0). Participants may be hospitalized to treat PM/DM.
b. It is strongly recommended that participants who permanently discontinue study drug, but do not withdraw from study participation, be followed at all subsequent study visits through Week 80.
   Participants, who permanently discontinue study drug administrations on or before the Week 72 visit, but do not withdraw from study participation, must undergo procedures for safety follow-up visits (postdiscontinuation) as outlined for the end of trial (EO-Treatment) visit as soon as possible on or before next scheduled visit.
   Participants, who permanently discontinue study drug administrations on or before the Week 72 visit, and withdraw from study participation, must undergo procedures for safety follow-up visits (postdiscontinuation) as outlined for the end of trial (EO-Treatment) visit as soon as possible on or before next scheduled visit, and must return approximately 8 weeks after last study drug administration to undergo procedures for safety follow-up visits (8 weeks postdiscontinuation) as outlined for the end of trial (EO-Treatment). If the interval between postdiscontinuation visit and 8 weeks postdiscontinuation visit is less than two weeks, can skip 8 weeks postdiscontinuation.
c. Participants, who discontinue study drug administrations on or before the Week 72 visit, and withdraw from study participation, must return approximately 16 weeks after last study drug administration to undergo procedures for safety follow-up visits as outlined for the end of trial (EO-Trial) visit.
d. Administration of study drug and visit window should be within ±7 days of the scheduled visit date. Unless otherwise specified, all assessments (except for injection-site evaluation) are to be completed prior to study drug administration.
e. Participants will sign informed consent forms for participation in the study CNTO1275DMY3001, and may additionally consent for the following: whole blood DNA collection for genetic factors at selected sites.
f. Participants should be performed cancer screening tests to exclude participants who meet exclusion criteria #45. The investigator should confirm the results of cancer screening tests brought by participants if they were performed at any other sites within 2 years.
g. IV administration of study drug at Week 0, IV and SC administration of study drug at Week 24 and all other doses will be SC to be administered at the study site through Week 72.
h. A 12-lead ECG will be performed locally. Participants should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs.
i. All assessments for ILD should be kept as close to the specified day as possible. If the investigator identifies new onset or worsening of ILD or observes any finding which needs to be evaluated by a pulmonologist, the investigator should consider consultation with a pulmonologist and administer rescue treatment as needed.
j. If any findings suggesting worsening or new onset of ILD are obtained, consultation with a pulmonologist is required. See Section 8.2.5.
k. Screening Chest x-ray posterior/anterior and lateral views must be taken for both ILD and TB detection.
l. Screening HRCT must be read by a radiologist or pulmonologist to evaluate the presence of ILD and TB.
m. TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray, chest HRCT, and T-SPOT.TB test or QFT should be performed.
n. In addition to the urine screening evaluation, a serum pregnancy test may be conducted at any time at the discretion of Investigator or participant. Urine pregnancy tests may be conducted more frequently (eg, monthly basis). Urine pregnancy tests may not be necessary if a subject is considered a postmenopausal state defined as no menses for 12 months without an alternative medical cause and a high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) during the study.
o. Participants should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection.
p. See Section 6.5.2 for information on glucocorticoid tapering.
q. ClinRO portion to be completed by the investigator at all sites.
r. It is recommended that MMT-8 be performed by an investigator who does not know the assessment result of participants including laboratory test.

s. Whenever possible, PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions.
t. FI-2 is recommended to be performed after MMT.
u. Assessments must be performed by the central laboratory unless otherwise indicated.
v. The same blood draw will be used for the measurement of ustekinumab concentration and detection of antibodies to ustekinumab. For visits with study drug administration, all blood samples for assessing predose ustekinumab concentration and antibodies to ustekinumab **MUST** be collected **BEFORE** the administration of the study drug. Residual sample may be used to evaluate antibodies to ustekinumab at unspecified visits or other biomarker analysis.
w. At Week 0, 2 separate samples for serum ustekinumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected prior to IV infusion and the other collected 1 hour after the end of the infusion) for all participants.
x. Additional venous blood sample collection for population PK analysis should occur on any day in each of the 2 designated time periods except on the days of scheduled study visits. Additionally, this blood sample should be collected at least 24 hours prior to or after the actual time of study drug administration.
y. Whole blood will be collected and processed for PBMC isolation and cryopreservation.
z. Whole blood for genetic analyses will be collected only from participants who sign a separate informed consent form to participate in the DNA substudy.

2. INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are chronic rheumatic diseases generally characterized by muscle weakness and low endurance. Most patients present with an insidious painless proximal symmetrical weakness. Other clinical features include pitting edema, pharyngeal muscle weakness causing hoarseness, dysphagia, and nasal regurgitation of liquids or aspiration pneumonia. Gastrointestinal symptoms can also consist of postprandial pain, distension, reflux, and diarrhea. There can be ventilatory muscle involvement (<5% of patients), which causes shortness of breath.[23] Skin features pathognomonic of DM are Gottron papules and a heliotrope rash. Gottron scaly erythematous or violaceous papules appear over bony prominences, mainly the metacarpophalangeal and proximal and distal interphalangeal joints of the hands. When this occurs over the extensor aspects of the knees, elbows, and ankles it is known as Gottron sign. The violaceous heliotrope rash erupts on the upper eyelids.[23] PM/DM often accompany other extramuscular involvements, such as interstitial lung diseases (ILDs), arthritis, and malignancies in adult patients.

Polymyositis and DM have been designated as an intractable disease by Ministry of Health, Labour and Welfare (MHLW) in Japan. There were 21,832 patients with PM/DM in Japan in 2016 based on the intractable disease registration database.

Glucocorticoids are used empirically as the first-line treatment, but have various adverse effects including glucocorticoid-induced myopathy. In addition, about a half of the patients with glucocorticoid monotherapy experience the relapse during glucocorticoid tapering.[28]

Various studies reported that concomitant treatment with steroid-sparing immunosuppressive agents, such as methotrexate (MTX), azathioprine (AZA), tacrolimus (TAC), cyclosporine A, and mycophenolate mofetil (MMF), was effective in idiopathic inflammatory myositis (IIM). The treatment guideline for PM/DM developed by the research group of Japan College of Rheumatology, The Japanese Dermatological Association, and Japanese Society of Neurology supports the use of MTX, AZA, TAC, cyclosporine A, MMF, and cyclophosphamide as immunosuppressants. Concomitant treatment with these agents reduces the relapse risk during glucocorticoid tapering.[20] However, effects are often disappointing and many patients are not able to regain muscle function.[4] Health-related quality of life in patients with PM/DM is low compared with the general population. The majority of commonly used drugs are not approved for myositis, and only few randomized controlled trials have been performed in this patient group. Existing therapies for PM/DM are generally either cytotoxic or immunosuppressive and may have notable safety risks. Thus, there is a large unmet need for new alternative treatments that can provide significant benefit in this disease without incurring a high safety risk.

The term "sponsor" used throughout this document refers to the entities listed in the ‘Protocol Supplementary Information’, which will be provided as a separate document.

2.1. Study Rationale

2.2. Background

To date, STELARA (ustekinumab) has received marketing authorization globally, for the treatment of adult and pediatric patients (age ≥12 to <18 years) with chronic moderate to severe plaque psoriasis, adult patients with active psoriatic arthritis (PsA), and adult patients with moderate to severe Crohn's disease. The cumulative global exposure (through 31 December 2018) has been estimated as 1,375,007 person-years. Based on completed clinical studies alone, 7,164 participants have been exposed to ustekinumab across all indications. In Phase 2 and Phase 3 clinical studies, participants have been exposed to ustekinumab for 6 months, 1 year, and some participants have had 5 or more years of exposure to the drug. The overall safety profile of ustekinumab was similar for patients regardless of indication and the most common adverse reactions (>5%) in controlled periods of clinical studies were nasopharyngitis and headache. Most adverse events (AEs) were considered mild and did not necessitate drug discontinuation.

Scientific Rationale for Use of Anti-Interleukin-12/23p40 Therapy in Polymyositis and Dermatomyositis

In the pathogenesis of myositis, interleukin (IL)-23 has attracted attention because some recent studies in humans and mice support the notion that IL-23 plays a role in PM/DM. The levels of IL-23 are increased in the serum and peripheral blood mononuclear cell (PBMC) of patients with PM/DM compared with healthy control subjects. By contrast, concentrations of IL-17 in PBMC from patients with PM/DM were not higher than those from healthy control subjects.[22] A study has reported detection of immature cluster of differentiation (CD)1a+ dendritic cells (DCs) and mature DC-LAMP positive and CD83+ DCs in association with the proinflammatory cytokines IL-17 and interferon (IFN)-γ in human muscle tissue of PM/DM.[17] In another study, muscle samples obtained from patients with PM/DM have shown expression of IL-23 (IL-23p19) messenger RNA (mRNA) and IL-17 mRNA though mRNA of these cytokines was not detected in muscle samples from healthy donors.[11] These studies indicate that IL-23/Th17 axis could be associated with pathogenesis of inflammatory myositis. A study of murine model of PM (C protein-induced myositis, CIM) has reported that serum concentration of IL-23 was elevated in myositis mice and that CD68+cells infiltrating into the lesions of myositis expressed IL-23.[27] Adoptive transfer of lymph node cells from myositis mice into IL-23 deficient mice successfully induced comparable myositis to wild type mice though IL-23 deficient mice themselves are resistant to CIM and do not develop myositis. It suggests that autoreactive lymphocytes induced in myositis mice play an important role in pathogenesis of myositis and that these pathogenetic lymphocytes are dependent on IL-23. In myositis mouse model, anti-IL-23R antibody ameliorated myositis therapeutically, which indicates that IL-23 would be the promising target for treatment of PM.

Interleukin-12 is known to be an important cytokine for the differentiation of Th1 cells. In addition, recent studies have shown IL-12 could induce IL-21 producing T follicular helper (Tfh) cell in a manner dependent on STAT4.[21] It has been reported that IL-21 expression is upregulated in patients with PM/DM in both serum[10] and muscle tissue.[12] The number of Tfh cells in patients

with IIM was increased compared to healthy control subjects.[6] These findings indicate IL-12 blockade could reduce the inflammatory response related to Tfh and IL-21.

Interleukin-12 and IL-23 secreted by DCs help to polarize Th1 and Th17 cells. The cytokines secreted by Th1 and Th17 cells such as IFN-γ, play some roles in development of myositis via upregulation of toll-like receptor 3 (TLR3) pathway.[25,26]

Ustekinumab is a fully human G1 kappa monoclonal antibody that binds with high affinity and specificity to the shared p40 subunit of human IL-12 and IL-23 cytokines. The binding of ustekinumab to the IL-12/23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer and CD4+ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including PM/DM. Therefore, inhibition of IL-12 and IL-23 has the potential to be effective in the treatment of PM/DM.

Though clinical usage of ustekinumab for PM/DM is limited, there is a case report of amyopathic dermatomyositis (ADM).[14] A 20-year-old male had a history of ADM which was refractory to multiple immunosuppressors. After developing psoriasis, the patient was treated with ustekinumab and has shown a very good clinical response.

Recent genome-wide association studies revealed considerable genetic overlap among immune-mediated inflammatory diseases including systemic lupus erythematosus (SLE) and some rheumatic diseases.[5] The findings show that autoantibody-mediated autoimmune diseases cluster more closely with each other than autoantibody-negative diseases such as psoriasis which form another genetic cluster. A meta-analysis shows a single nucleotide polymorphism is associated with susceptibility to several autoimmune diseases including SLE and myositis.[31] A genome-wide gene expression analysis has revealed overlap of gene expression signature including interferon between DM and lupus, which is distinct from other inflammatory skin diseases.[30] Another genome-wide association study in DM has confirmed the importance of the major histocompatibility complex (MHC) complex but also suggested non-MHC genetic features overlapped with other autoimmune diseases including SLE.[13] These findings indicate the potential overlap of pathogenesis between SLE and myositis.[30]

A Phase 2a trial has shown that administration of ustekinumab in patients with SLE improved disease activity scores and reduced autoantibody titer. The results from studies in animal models, human translational and genetic studies also support a role of IL-12/23p40 as a therapeutic target in pathogenesis of PM/DM.

Taken together, these findings indicate that blockade of IL-12/IL-23 would be a promising target for the treatment of PM/DM.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure (IB) for ustekinumab.[9]

2.3. Benefit/Risk Assessment

To date, ustekinumab has received marketing authorization globally for the treatment of adult and pediatric patients (age ≥12 to <18 years) with chronic moderate to severe plaque psoriasis, adult patients with active PsA, and adult patients with moderate to severe Crohn's disease. Japan has received marketing authorization approval of ustekinumab for the treatment of moderate to severe psoriasis and PsA in January 2011 and for the treatment of Crohn's disease in March 2017.[9]

The overall safety profile of ustekinumab was similar for patients regardless of indication. Refer to the latest version of the IB for further details.[9]

In this Phase 3 study, potential risks of treatment with ustekinumab (eg, serious infections including tuberculosis (TB) and hypersensitivity reactions), as well as the potential risks inherent in patients with PM/DM (ILD, serious infections, arteriosclerotic diseases, and malignancies), are being addressed in multiple ways:

- Inclusion/exclusion criteria (Section 5.1 and 5.2) set limits regarding, for example, history of unstable or progressive organ-threatening disease, infections or predisposition to infections, history of reactions to biologic agents, and baseline laboratory abnormalities.
- Comprehensive medical monitoring of data by the sponsor during the conduct of this study includes regular assessment of AEs and serious adverse event (SAEs), vital signs, physical examination, and laboratory results and evaluation for ILD using chest x-ray, high-resolution computer tomography (HRCT), and pulmonary function test (PFT) (Section 1.3, Schedule of Activities) to evaluate individual cases as well as potential emerging safety trends. In addition, as discussed in Section 9.5.1, an external independent data monitoring committee (IDMC) will provide oversight and will conduct independent evaluation of the safety data accrued in this protocol.
- Certain concomitant medications have been prohibited (Section 6.6) and limitations set on dose levels of permitted concomitant medications, such as high dose glucocorticoids, cytotoxic agents, and use of multiple biologics simultaneously, that could introduce safety risks due to oversuppression of the immune system.
- The steroid-sparing effects of ustekinumab are being evaluated by implementing a glucocorticoid taper from Week 2 to Week 16 and from Week 24 to Week 80. This may add benefit by reducing the risk of infection and other glucocorticoid-related complications. However, should a participant experience worsening of disease activity, rescue therapy is permitted per medical necessity as outlined in Section 6.5.5.

Based on the available safety data from clinical trials and postmarketing experience including other disease indications, and proposed safety measures, the overall risk/benefit assessment of ustekinumab in this protocol is acceptable.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

The primary objective is 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).

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

ENDPOINTS

Primary Endpoint

The primary endpoint is the proportion of participants who achieve Minimal Improvement in International Myositis Assessment and Clinical Studies Total Improvement Score (IMACS TIS) at Week 24.

Secondary Endpoints

The secondary endpoints are:

- Mean change from baseline in Functional Index-2 (FI-2) at Week 24
- The proportion of participants who experience disease worsening through Week 24 based on consensus criteria for worsening
- Mean change from baseline in Manual Muscle Testing (MMT)-8 at Week 24
- Mean change from baseline in PhGA at Week 24
- Mean change from baseline in Extramuscular Assessment (Myositis Disease Activity Assessment Tool [MDAAT]-Extramuscular Global Assessment) at Week 24

- Mean change from baseline in muscle enzymes (creatine kinase [CK], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and aldolase) at Week 24

Tertiary Endpoints

PM/DM Disease Activity

- The proportion of participants who achieve Minimal Improvement in IMACS TIS over time
- 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
- Mean change from baseline in PhGA over time
- The proportion of participants with improvement in PhGA 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

Patient-reported Outcomes

- Mean change from baseline in Patient Global Activity (PtGA) at Week 24
- The proportion of participants with improvement in PtGA 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 over time
- The proportion of participants with improvement in PtGA 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

Pharmacokinetics and Immunogenicity

- Summary of serum ustekinumab concentrations
- Incidence of anti-ustekinumab antibodies

Biomarkers

- Biomarkers of ustekinumab treatment response over time

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

Treatment with ustekinumab is superior to placebo in participants with active PM/DM despite receiving 1 or more standard-of-care treatments as measured by the proportion of participants achieving IMACS TIS at Week 24.

4. STUDY DESIGN

4.1. Overall 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 a 16-week safety follow-up period.

Approximately 50 participants will be randomly assigned in a 1:1 ratio to receive either ustekinumab or matching placebo with the following treatment administrations (see Section 6 for further details of study drug administration):

- Week 0: Body weight-range based intravenous (IV) administration of ustekinumab (~6 mg/kg) or placebo
- Week 8 and Week 16: Ustekinumab 90 mg subcutaneous (SC) administration or placebo
- Week 24: Placebo group participants crossover to receive body weight-range based IV administration of ustekinumab (~6 mg/kg) and placebo SC and ustekinumab group participants receive placebo IV and continue with SC administration of 90 mg ustekinumab
- Week 32, Week 40, Week 48, Week 56, Week 64, and Week 72: SC administration of 90 mg ustekinumab

A placebo comparator (in addition to standard-of-care background therapy) will be used in this study through Week 24 to allow for blinded, placebo-controlled evaluation of the efficacy and safety of ustekinumab in participants with PM/DM.

Randomization 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]) using permuted block central randomization.

The primary efficacy analysis will be performed after all participants have completed Week 24 efficacy assessments (or discontinued) with additional secondary endpoints to be analyzed at Week 24.

Four database locks (DBLs) will occur 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. Investigative study sites and participants will remain blinded to initial treatment assignment until the DBL at Week 52. After the Week 24 DBL, the data will be unblinded to sponsor for analysis while 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. 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.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol (see Section 6.5.2 for information on glucocorticoid tapering). Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

An external IDMC will be commissioned for this study. Refer to Section 9.5.1 for further details.

A futility analysis will be carried out after 20 participants complete Week 24 visit. The analysis will be performed in an unblinded fashion by the IDMC based primarily on Week 24 efficacy data. The details of the futility analysis will be included in the interim analysis plan.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical or surrogate endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical and surrogate endpoints.

Biomarker and Pharmacogenomics Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the PK, efficacy, safety, or tolerability of ustekinumab and to identify genetic factors associated with PM/DM.

Biomarker samples will be collected to evaluate the mechanism of action of ustekinumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention.

A pharmacogenomic blood sample (whole blood DNA) will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

Biomarker and DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Vulnerable populations (ie, persons in detention) are not eligible for this study.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Japan Red Cross (400 mL x 2~3 times/year of blood for donation).

4.3. Justification for Dose

Higher doses and more frequent administration have generally resulted in greater proportions of patients achieving higher levels of response across disease indications. The planned regimen in this trial is the highest and most frequent regimen in the approved indication (Crohn's disease) as well as ongoing Phase 3 studies (ulcerative colitis and SLE). Given the multi-organ systemic involvement of PM/DM, higher exposures enabled by IV dosing and resultant more rapid onset of action might be important in maximizing efficacy in PM/DM. In addition, safety data of the planned regimen (in combination with standard treatment including systemic glucocorticoids and immunosuppressant agents) were obtained and analyzed in previous clinical trials in participants with Crohn's disease, ulcerative colitis, or SLE. The existing safety data from these studies using the same dosing regimen will provide evidence of the safety of the selected dose in this trial.

Similar clinical features are observed in PM/DM and SLE. Genome-wide association studies indicate the potential overlap of pathogenesis between myositis and SLE, and biomarker findings also suggest similarity between DM and SLE. Standard treatments for SLE include systemic glucocorticoids and immunosuppressants, which are also common treatments for PM/DM. Results from a Phase 2 study of ustekinumab in SLE has suggested the effectiveness of ustekinumab in patients with SLE. PK parameters of ustekinumab have, in general, been similar across multiple indications, including psoriasis, PsA, Crohn's disease, and SLE after correcting for body weight-related PK differences. Study CNTO1275SLE2001 has shown that treatment with ustekinumab administered as an ~6 mg/kg IV dose following by 90 mg SC dose at Week 8 and then every 8 weeks thereafter was efficacious and generally well tolerated in subjects with SLE. The safety profile of this dose regimen in the CNTO1275SLE2001 study was consistent with the well-established profile observed in several large-scale Phase 3 Crohn's disease studies. Taking the overlapping features of PM/DM and SLE into account, the planned regimen may be effective in patients with PM/DM.

4.4. End of Study Definition

The end of study is considered as the last follow-up assessment at Week 88 for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of all Week 88 assessments of the last participant at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study drug. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedure is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Be male or female (according to their reproductive organs and functions assigned by chromosomal complement).

2. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

3. Must sign a separate ICF (or their legally acceptable representative must sign) if he or she agrees to provide an optional DNA sample for research. Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study

4. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5. Be between 18 and 75 years of age, inclusive.

6. Must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, other specific tests, blood coagulation, hematology, or urinalysis except for items specified in Inclusion Criteria #20 and 21 are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initiated by the investigator.

7. Has a diagnosis of PM/DM made or confirmed by a physician (such as a rheumatologist, neurologist, or dermatologist) experienced in treatment of PM/DM.

8. Has a documented medical history that participant met the diagnostic criteria of probable or definite IIM based on 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies at least 6 weeks prior to first dose of the study drug.

   If a participant with PM did not have history of muscle biopsy, score of classification cannot be calculated. If a participant with DM did not have history of muscle biopsy, score of classification must be calculated based on score without muscle biopsy. In addition, the diagnosis based on subclassification criteria must be 1 of following;

- PM, DM

9. Demonstrable muscle weakness at screening and Week 0 measured by the MMT-8 of ≤135 units.

10. Demonstrable muscle weakness at screening measured by any 2 or more of the followings:

- PhGA ≥1.5 cm
- 1 or more muscle enzymes (CK and aldolase) ≥1.4×upper limit of normal (ULN)
- MDAAT-Extramuscular Global Assessment ≥1.5 cm

11. Has PM or DM which is considered active despite receiving at least 1 standard-of-care treatment by the investigator.

12. Criterion modified per Amendment 2:

12.1 Must be receiving 1 or more of the following protocol-permitted, systemic standard-of-care treatments:

- If using oral glucocorticoids, must be administered for ≥6 weeks and at a stable dose for ≥2 weeks prior to first dose of the study drug. If not receiving immunomodulatory drugs and only using oral glucocorticoid as standard treatment, its daily dose must be between 0.25 mg/kg and 1.0 mg/kg of prednisolone or equivalent at first dose of the study drug.

If currently not using oral glucocorticoids, must not have received them for ≥6 weeks prior to the first dose of the study drug.

- If using 1 or 2 of the following immunomodulatory drugs within the range of maximum dose or concentration, must be receiving all of those for ≥8 weeks and be on a stable dose for ≥4 weeks prior to first dose of the study drug:

  MMF ≤3 g/day

  AZA 1 to 2 mg/kg/day; up to 3 mg/kg/day

  Oral MTX ≤15 mg/week with concomitant folic acid or calcium folinate

  Oral TAC targeting trough concentration of 5 to 10 ng/mL

  Oral cyclosporine A targeting trough concentration of 100 to 150 ng/mL

13. Criterion modified per Amendment 2:

13.1 Regular or as needed treatment with topical use of glucocorticoids are permitted to treat skin lesions on a stable dose for ≥2 weeks prior to first dose of the study drug (see Section 6.5.4. for potency of topical glucocorticoids).

14. Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

    Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

    A woman must be (as defined in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information),

    a. Not of childbearing potential
    b. Of childbearing potential and
        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method throughout the study and for at least 16 weeks after the last dose of the study drug-the end of relevant systemic exposure. Examples of highly effective methods of contraception are described in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
        - Pregnancy testing (serum or urine) at the end of study intervention.

    Note: If childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, or a premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above.

15. A woman of childbearing potential must have a negative highly sensitive serum/urine (β human chorionic gonadotropin [β-hCG]) obtained during screening and at Week 0 before the first dose of the study drug.

16. A woman using oral contraceptives must use an additional contraceptive method (above that required in Inclusion Criterion #14).

17. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 4 months after receiving the last dose of the study drug.

18. When a man engaging in any activity that allows for passage of ejaculate to another person and a man has not had a vasectomy, he must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. All men must not donate sperm for the purpose of reproduction during the study and for 20 weeks after receiving the last dose of the study drug.

Note: Use should be consistent with local regulations regarding the use of contraceptive methods for participants.

19. Are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB prior to screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB at least 3 weeks prior to the first administration of the study drug, or have documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of the study drug. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.

    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB at least 3 weeks prior to the first administration of the study drug.

    d. Within 6 weeks prior to the first administration of the study drug, has a negative interferon gamma release assays (IGRAs) result, or have a newly identified positive IGRAs result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of the study drug. A participant whose first IGRA result is indeterminate should have the test repeated. In the event that the second IGRA result is also indeterminate, the participant should be excluded from the study.

    NOTE: IGRA is not required at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; Participants with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

    e. Have a chest radiograph (both posterior-anterior and lateral views) or chest CT, taken within 3 months prior to the first administration of the study drug and read by a radiologist or pulmonologist, with no evidence of current, active TB or old, inactive TB.

20. Participants must have laboratory test results within the following parameters at screening:

    - Hemoglobin ≥8.0 g/dL (International System of Units [SI]: ≥80 g/L)
    - Lymphocytes ≥0.5×103/μL (SI: ≥0.5 GI/L)
    - Neutrophils ≥1.5×103/μL (SI: ≥1.5 GI/L)

- Platelets ≥75×103/μL (SI: ≥75 GI/L)
- Serum creatinine ≤1.92 mg/dL (SI: ≤170 μmol/L)

21. The AST and ALT levels must be within 3×ULN range for the laboratory conducting the test, except that elevation of AST or ALT is considered directly due to disease activity of myositis by the investigator based on muscle enzyme (CK or aldolase) levels.

22. A one-time repeat of these screening laboratory tests (ie, hemoglobin, lymphocytes, neutrophils, platelets, serum creatinine, AST, and ALT) is allowed during the 6-week screening period and the investigator may consider the participant eligible if the previously abnormal laboratory test result is within an acceptable range on repeat testing at the central laboratory. A screening laboratory test analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the 6-week screening period.

23. Participants with other marked disease-associated laboratory abnormalities may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator. Participants with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or Grade 4 laboratory abnormalities must be discussed with the sponsor to determine eligibility for enrollment.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Has myositis other than PM/DM, including but not limited to ADM, clinically amyopathic DM, juvenile DM, inclusion body myositis (IBM), immune-mediated necrotizing myopathy diagnosed based on muscle biopsy findings and positive anti-SRP or anti-HMGCR antibody, drug-induced myositis, PM associated with human immunodeficiency virus (HIV), muscular dystrophy, congenital myopathy, metabolic myopathy, and mitochondrial myopathy.

2. Has other inflammatory diseases that might confound the evaluations of efficacy, including but not limited to rheumatoid arthritis (RA), PsA, SLE, psoriasis, or Crohn's disease.

3. Has severe or progressive ILD, which was confirmed by the investigator based on HRCT findings, clinical course consistent with ILD, and consultation with a pulmonologist. Findings from HRCT at screening should not show clinically significant worsening compared to past HRCT or comparable CT results taken at least 3 months

before screening. The eligibility of ILD may be determined considering the following but not limited to;

- Presence of dyspnea on exertion with normal activities of daily living or low grade exertion (eg, walking), or a recent change in exercise tolerance due to dyspnea
- Partial pressure of oxygen in arterial blood (PaO2) of less than 80 mm Hg while breathing ambient air at rest, not accompanied by abnormal increase of PaCO2
- Vital capacity (VC) <80% predicted, or diffusing capacity of the lungs for carbon monoxide (DLCO) <65% predicted

4. Has positive test result of anti-MDA5 antibody (anti-CADM-140 antibody).

5. Has severe respiratory muscle weakness confirmed by the investigator based on the consultation with a pulmonologist and the measures of respiratory muscle strength such as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) and/or maximal voluntary ventilation (MVV) measurements and lung capacity such as forced vital capacity (FVC). The results need to be within population appropriate normal limits.

6. Has severe muscle damage (Myositis Damage Index-VAS [Muscle Damage] >7 cm), permanent weakness due to a nonIIM cause, or myositis with cardiac dysfunction.

7. Has glucocorticoid-induced myopathy which the investigator considers the primary cause of muscle weakness.

8. Is pregnant, nursing, planning a pregnancy, or planning to father a child while enrolled in the study or within 4 months after receiving the last administration of the study drug.

9. Is an employee of the investigator or study site (ie, personnel to whom the investigator has delegated a role or responsibility for conducting the study), with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

10. Lives in an institution on court or authority order, unless permitted by local regulations.

11. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Concomitant or previous medical therapies received:

12. Has received systemic immunomodulatory agents other than those described in inclusion criteria within 8 weeks or 5 half-lives, whichever is longer, prior to the first dose of the study drug. Glucocorticoids are not included in this criterion; see Section 6.5.2 regarding glucocorticoid use.

13. Has used oral cyclophosphamide within 12 weeks or IV cyclophosphamide within 24 weeks prior to the first dose of the study drug.

14. Has ever received ustekinumab.

15. Has received prior IV immunoglobulin (Ig) or immunomodulatory biologic therapy not described in Section 6.6, Prohibited Therapies such as guselkumab, risankizumab, belimumab, epratuzumab, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, or agents whose mechanism of action targets B cell, tumor necrosis factor alpha (TNFα), IL-1, IL-2, IL-6, IL-17, IL-23, or IFN pathways, within 5 half-lives or 12 weeks, whichever is longer, prior to first dose of the study drug. Has received rituximab within 24 weeks prior to first dose of the study drug.

16. Has received adrenocorticotropic hormone (ACTH) administered by injection within 1 month prior to the first administration of the study drug.

17. Has received topical immunomodulatory agents (such as tacrolimus, cyclosporine A) within 4 weeks prior to the first dose of the study drug.

18. Has received an investigational drug that is not previously defined in other exclusion criteria (including investigational vaccines, branched-chain amino acids, or other medications specified in Section 6.6) within 5 half-lives or 12 weeks, whichever is longer, or used an invasive investigational medical device within 12 weeks before the planned first dose of the study drug, or is currently enrolled in an interventional study.

19. Is currently receiving allergen immunotherapy such as cedar pollen.

20. Participants likely to require multiple courses of systemic glucocorticoids for reasons other than PM/DM (eg, uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, etc) should be excluded from study participation.

21. Has received epidural, IV, SC, intramuscular (IM), intra-articular, intrabursal, or intralesional administration of glucocorticoids within 6 weeks prior to the first administration of the study drug.

22. Use of apheresis therapy (including but not limited to plasmapheresis, photopheresis, leukocytapheresis), or immunoadsorption is prohibited within 24 weeks prior to the first administration of the study drug.

23. Has ever received stem cell transplantation (including hematopoietic stem cell transplantation and mesenchymal stem cell transplantation).

Infections or predisposition to infections:

24. Has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

25. Has received a live virus or live bacterial vaccination within 16 weeks prior to the first administration of the study drug.

26. Has a history of active granulomatous infection, including histoplasmosis, or coccidioidomycosis. Refer to Section 5.1 for information regarding eligibility with a history of latent TB.

27. Has a chest radiograph or chest HRCT within 3 months prior to the first administration of the study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB. Radiographic findings such as pulmonary nodules should be evaluated by an experienced radiologist and/or pulmonologist to determine whether the presentation is suggestive of infection or active malignancy and final assessment documented by the investigator prior to randomization.

28. Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

29. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), chronic infectious sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis), an open, draining, or infected skin wound or ulcer.

30. Has a history of HIV antibody positive, or tests positive for HIV at screening.

31. Has a hepatitis B infection. Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody total (anti-HBc total).

32. Is seropositive for antibodies to hepatitis C virus (HCV), unless has 2 negative HCV ribonucleic acid (RNA) test results 6 months apart prior to screening and has a third negative HCV RNA test result at screening.

33. Has experienced a recent single dermatomal herpes zoster eruption within the past 4 months or has experienced multiple eruptions of herpes zoster within the past 18 years. Has ever had multi-dermatomal herpes zoster (defined as appearance of lesion outside the primary or adjacent dermatome) or central nervous system zoster infection.

34. Within 2 months prior to the first administration of the study drug, has had a serious infection (eg, pneumonia, sepsis, or pyelonephritis), or has been hospitalized for an infection, or has been treated with IV antibiotics for an infection. Less serious infections

(eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

Concurrent medical conditions or past medical history and procedures:

35. Has a known hypersensitivity to human Ig proteins (eg, IV Ig).

36. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (see Section 6.1and the ustekinumab IB[9]).

37. Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, significant cardiac, vascular, hematologic, gastrointestinal, endocrine, pulmonary, neurologic, rheumatologic, immunologic, psychiatric, metabolic disturbances), disease of any organ system, or active acute or chronic infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the participant if he or she participates in the study.

38. Has advanced chronic kidney disease such as end-stage renal disease or receives hemodialysis.

39. Has past history of severe ILD flare, severe non-infectious lung inflammation which required active intervention (systemic glucocorticoid or other immunomodulators), or multiple relapses of these conditions.

40. Has had major surgery, (eg, requiring general anesthesia) within 1 month before screening, or will not have fully recovered from surgery, or has major surgery (eg, requiring general anesthesia) planned during the time the participant is expected to participate in the study or within 1 month after the last dose of the study drug administration.

    Note: Participants with planned minor surgical procedures to be conducted under local anesthesia may participate after discussion with the sponsor.

41. Has a transplanted organ (except for a corneal transplant performed >3 months prior to the first administration of the study drug).

42. Has or has had a substance abuse (drug or alcohol) problem within the previous 3 years.

43. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy venous access.

Malignancy or increased potential for malignancy:

44. Presence or history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin that has been treated with no evidence

of recurrence for at least 3 months before the first study drug administration and carcinoma in situ of the cervix that has been documented to be surgically cured).

45. Has positive cancer screening test dependent on the status of anti-TIF1-γ antibody as follows;

    - Has negative test result for anti-TIF1-γ antibody and positive cancer screening test provided by local governments or equivalent test (Section 10.7, Appendix 7: Cancer Screening Test) including gastric cancer, lung cancer, cervical cancer, breast cancer, and/or colon cancer within 2 years before the first study drug administration if the age and sex of participants are qualified.
    - Has positive test result for anti-TIF1-γ antibody and positive cancer screening test provided by local governments (Section 10.7, Appendix 7: Cancer Screening Test) including gastric cancer, lung cancer, cervical cancer, breast cancer, and/or colon cancer within 2 years before the first study drug administration irrespective of age if the sex of participants is qualified.

46. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, clinically significant splenomegaly, history of splenectomy, or history of monoclonal gammopathy of undetermined significance.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of the study drug is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. The sponsor reserves the right to discontinue the participant for any operational or safety reasons.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Agree to avoid vigorous intensity exercise such as running, contact sports, and weight training throughout the study.

2. Agree to avoid starting exercise therapy throughout the study. In case participants already receive exercise therapy regularly before screening, they must not change the intensity and frequency of exercise therapy throughout the study.

3. Agree to use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen), limit prolonged exposure to natural sunlight, and avoid artificial sunlight

(tanning beds or phototherapy) from baseline until the last dose of the study drug for participants with DM.

4. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

5. Agree not to receive a live virus or live bacterial vaccination during the study. Subjects must also agree not to receive BCG vaccination for 12 months after last dose of study agent, or any other live vaccine for 16 weeks after receiving the last administration of study agent.

6. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Rescreening

A one-time repeat of screening laboratory tests (eg, hemoglobin, lymphocytes, neutrophils, platelets, serum creatinine, AST, and ALT) and screening imaging tests (chest x-ray and HRCT) is allowed during the 6-week screening period and the investigator may consider the participant eligible if the previously abnormal laboratory test result or imaging finding is within an acceptable range on repeat testing at the central laboratory. A screening laboratory tests analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the 6-week screening period. A screening imaging test may be repeated once after a period of at least 30 days.

The goal of the retest procedure is to assess if the participant is eligible for randomization within the screening window or is a screen failure. Participants who have laboratory values that do not meet entry criteria following the retest or do not meet disease activity criteria following the repeat procedure are to be deemed screen failures. Exceptions to this are positive IGRAs, hepatitis C or B, or HIV tests; unless there is a suspected error in sample collection or analysis performance, these tests may not be repeated to meet eligibility criteria.

If a participant is a screen failure, the participant may be rescreened 1 additional time after a period of at least 30 days. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process again, and restart a new screening phase with carrying screening test results over from previous screening if appropriate.

6. STUDY DRUG

6.1. Study Drugs Administered

Intravenous Administration

Ustekinumab supplied for this study is a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). In addition to ustekinumab, the solution contains 10 mM L-histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate at pH 6.0. No preservatives are present.

Placebo administrations will have the same appearance as the respective ustekinumab administrations. Matching placebo for final vialed product (IV) is supplied as single-use, sterile solution in 30 mL vials with a 26 mL nominal volume. The composition of the placebo is 10 mM L-histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL EDTA disodium salt dihydrate at pH 6.0. No preservatives are present.

Subcutaneous Administration

Ustekinumab will also be supplied as a single-use prefilled syringe (PFS) in a strength of 90 mg in 1 mL nominal volume for SC administration. Each 1 mL of ustekinumab solution in the PFS contains 90 mg ustekinumab with nominal excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Placebo administrations will have the same appearance as the respective ustekinumab administrations. Liquid placebo will also be supplied in a 1 mL PFS, and have a composition 10 mM L-histidine, 8.5% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

The study drug administration must be captured in the source documents and the electronic case report form (eCRF.)

Ustekinumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[9]

Dosage Administration

Following randomization at Week 0, participants assigned to the active treatment group will receive an initial body weight-range based IV dose ~6 mg/kg of ustekinumab (ustekinumab

260 mg weight ≤55 kg; ustekinumab 390 mg weight >55 kg and ≤85 kg; ustekinumab 520 mg weight >85 kg), and participants who were randomized to placebo will receive a single IV dose of placebo. Starting at Week 8, participants will receive SC dosing with either placebo or ustekinumab 90 mg q8w through Week 24. At Week 24, participants receiving placebo will crossover to receive body weight-range based IV administration of ustekinumab. At Week 24, it is recommended that SC dosing is administrated after completion of IV administration. SC dosing may be administered before assessment of infusion reactions. However, IV and SC administration to the same limb should be avoided. Starting at Week 32, all participants will receive ustekinumab 90 mg SC q8w through Week 72.

Week 0 up to Week 16

Group 1: Participants will receive body weight-range based IV dosing of ~6 mg/kg of ustekinumab at Week 0 followed by ustekinumab 90 mg SC administrations at Weeks 8 and 16.

Group 2: Participants will receive IV dosing of placebo at Week 0 followed by placebo SC administrations at Weeks 8 and 16.

Week 24

Group 1: Participants will receive IV dosing of placebo and ustekinumab 90 mg SC administration.

Group 2: Participants will receive body weight-range based IV dosing of ~6 mg/kg of ustekinumab and placebo SC administration.

Week 32 up to Week 72

Groups 1 and 2: Participants will receive ustekinumab 90 mg SC q8w administrations through Week 72.

Description of Interventions

Arm Name	Group 1	Group 1	Group 1/2	Group 2	Group 2	Group 2
Intervention Name	Ustekinumab	Ustekinumab	Placebo	Placebo	Ustekinumab	Ustekinumab
Type	Study drug					
Dose Formulation	a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume)	a single-use PFS for SC administration	single-use, sterile solution in 30 mL vials with a 26 mL nominal volume	a single-use PFS for SC administration	a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume)	a single-use PFS for SC administration
Dosage Level(s)	At Week 0 Body weight-range based IV dosing*	At Week 8 and q8w through Week 72 90 mg	At Week 24(Group1) At Week 0(Group 2) Body weight-range based IV dosing*	At Week 8 and 16 90 mg	At Week 24 Body weight-range based IV dosing*	At Week 32 and q8w through Week 72 90 mg
Route of Administration	IV	SC	IV	SC	IV	SC
Use	Treatment	Treatment	To maintain the blind (Group 1) Placebo-comparator (Group 2)	Placebo-comparator	Treatment	Treatment
Sourcing	Provided centrally by the Sponsor					
Packaging and Labeling	The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. The study drug will be packaged in individual participant kits. Each kit will consist of a single vial or PFS packaged inside a protective outer carton.					
Child Resistant or Not	Not in child resistant packaging					

*The body weight-range based doses are based on the following:
Body weight ≤55 kg: 260 mg ustekinumab (2 vials)
Body weight >55 kg and ≤85 kg: 390 mg ustekinumab (3 vials)
Body weight >85 kg: 520 mg ustekinumab (4 vials)

6.2. Preparation/Handling/Storage/Accountability

All study drug must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C).

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on the study drug preparation, handling, and storage.

The investigator is responsible for ensuring that all the study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the participant must be documented on the study drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, will be documented on the intervention return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

The study drug should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. The study drug will be supplied only to participants participating in the study. Returned study drug must not be dispensed again, even to the same participant. The study drug may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Drug Allocation

Procedures for Randomization and Stratification

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. Investigative study sites and participants will remain blinded to initial treatment assignment until the DBL at Week 52. After the Week 24 DBL, the data will be unblinded to sponsor for analysis while 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. 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.

6.4. Study Drug Compliance

Study site personnel will maintain a log of all the study drug administered. Drug supplies for each participant will be inventoried and accounted for. 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).

Additional details may be provided in a pharmacy manual/study site investigational product and procedures manual that is provided separately and noted in Study-Specific Materials in Section 8, Study Assessments and Procedures.

6.5. Concomitant Therapy

All prestudy therapies administered up to 12 weeks before entry into screening must be recorded at screening. Detailed information of prestudy topical and systemic PM/DM therapies including dosage and frequency of administration must be recorded. For any therapies that were discontinued, the reason for discontinuation (eg, no response, loss of response, intolerance, safety concern, etc) should be documented. Modification of an effective preexisting therapy must not be made for the explicit purpose of entering a participant into the study.

Concomitant PM/DM therapies and concomitant therapies for indication other than PM/DM must be recorded throughout the study beginning with start of the first dose of study drug until 8 weeks after the last dose of study drug. Concomitant therapies should also be recorded beyond 8 weeks after the last dose of the study drug only in conjunction with new or worsening AEs, SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including polypeptide/amino acid agent, vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Every reasonable effort should be made to keep concomitant medications, except for glucocorticoid (Table 1 and Table 2), stable to avoid introducing non-protocol medications for PM/DM disease activity through Week 24 or as specified in the following sections. Dose stabilization of all concomitant medications is required prior to randomization (Section 6.5.1, Prestudy and Concomitant Medications Through Week 80). All medications for the treatment of PM/DM must meet study protocol guidelines (see Section 6.5.1, Prestudy and Concomitant Medications Through Week 80). It is recommended that all other concomitant medications be maintained at stable doses through Week 24 or through the 8-week safety follow-up for those discontinuing the study prematurely on or before the Week 24 visit. If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the participant's medical record. Adjustments in concomitant therapies (Section 6.5.2, 6.5.3, and 6.5.4) that do not comply with the study protocol guidelines should not allowed through Week 80.

During the entire study, investigators should consider whether increases in permitted background therapy due to increased PM/DM disease activity warrant discontinuation of the study drug. This

should be discussed with the sponsor. If protocol-prohibited immunosuppressants, biologics (such as abatacept or rituximab), cytotoxic agents (such as cyclophosphamide), Ig agent (such as venoglobulin), IV glucocorticoids, apheresis therapy, or high average daily doses of oral glucocorticoids (≥1 mg/kg/day of prednisolone or equivalent) are initiated for severe, progressive, or unstable PM/DM disease activity (eg, Progressive ILD), the participant should be discontinued from the study.

See Section 6.5.2 for management of glucocorticoid therapy through Week 80.

6.5.1. Prestudy and Concomitant Medications Through Week 80

Limitation of concomitant medications must be followed through Week 80.

6.5.2. Glucocorticoid Therapy

Table 1 outlines oral glucocorticoid dose stabilization requirements prior to randomization and allowable dosing during study period. Changing the kind of glucocorticoid is allowed as long as it is the same equivalent dose. If participants have glucocorticoid-induced side effects such as osteoporosis and hyperglycemia, they need to be treated properly in the judgment of the investigator.

Table 1: Prestudy and Concomitant Glucocorticoid Use Through Week 80

Study period	Allowable dose
Before randomization	Daily dose must be ≥0.25 mg/kg of prednisolone or equivalent for ≥6 weeks with stable dosing ≥2 weeks prior to the first dose of the study drug. Daily dose is allowed up to 1 mg/kg of prednisolone or equivalent at randomization.
Week 0 through Week 2	No adjustments in glucocorticoid dose are permitted.
Week 2 through Week 16	Glucocorticoid dose needs to be reduced based on the table of glucocorticoid tapering schedule (See Table 2). Reduction of glucocorticoid dose should follow study drug administration at the weeks of study drug administration. If current daily prednisolone or equivalent dose is ≥50 mg, the dose will be reduced by 10 mg. If current prednisolone or equivalent dose is <50 mg and ≥20 mg, the dose will be reduced by 5 mg. If current prednisolone or equivalent dose is <20 mg and ≥12.5 mg, the dose will be reduced by 2.5 mg. If current prednisolone or equivalent dose is <12.5 mg and ≥6 mg, the dose will be reduced by 1 mg. Once the daily prednisolone or equivalent dose reaches 5 mg, the reduction of glucocorticoid is not necessary and can be done at the investigator's discretion. Increase in glucocorticoid dose up to baseline dose (Week 0) is permitted only once through Week 16 after discussion with the sponsor. Continuing the same glucocorticoid dose is permitted only once for less than consecutive 6 weeks.
Week 16 through Week 24	No adjustments in glucocorticoid dose are permitted.
Week 24 through Week 80	Dose adjustment in glucocorticoid is allowed at the investigator's discretion as long as the glucocorticoid dose does not exceed the baseline. Glucocorticoid dose reductions are strongly encouraged.

Table 2: 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

6.5.3. Non-biologic Immunomodulators

Participants are allowed to use up to 2 of the following immunomodulatory drugs without any change in dose from baseline (Week 0) through Week 24. Dose adjustment in immunomodulator is allowed at the investigator's discretion after Week 24 as long as the dose does not exceed the baseline.

- MMF
- AZA
- Oral MTX
- Oral TAC
- Oral cyclosporine A

6.5.4. Topical Medications

For the treatment of cutaneous lesion in participants with PM/DM or other concurrent medical conditions, regular use of topical medications is permitted. However, topical compounds cannot include a prohibited medication. Topical glucocorticoids must be medium/mild (Group IV) or weak (Group V) potency glucocorticoids to treat cutaneous lesions of myositis or skin disease of the same area as cutaneous lesions of myositis. Topical glucocorticoids may be very strong (Group II) or weaker potency glucocorticoids to treat cutaneous lesions of other concurrent medical conditions whose area is different from cutaneous lesions of myositis. "As needed" use of topical glucocorticoids is permitted, but not within 48 hours prior to a study visit for efficacy assessment. The investigator should notify the sponsor if topical glucocorticoids of very strong (Group II) or weaker potency are used on skin lesion up to 2 weeks where there is no preexisting skin eruptions of myositis in case it is considered due to adverse events other than cutaneous lesions of myositis.

6.5.5. Rescue Medication

The following rescue medications may be used if the investigator confirms the worsening of myositis in such cases of evident elevation of muscle enzymes and the necessity of additional treatment:

- Increase in glucocorticoid dose up to baseline dose is permitted only once after discussion with the sponsor.
- Continuing the same glucocorticoid dose is permitted only once for less than consecutive 6 weeks.

The use of rescue medications is allowable at Week 2 through Week 16 following the administration of study drug. The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6. Prohibited Therapies

Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Sections 5.1 and 5.2), are prohibited until Week 80 visit or 8 weeks safety follow-up including, but not limited to, the following:

- B-cell targeting agents (anti-CD20 eg, rituximab, anti-B-cell activating factor [BAFF], also known as B lymphocyte stimulator [BLyS], eg, belimumab, or anti-CD22 eg, epratuzumab, or other B-cell targeting therapies, such as tabalumab, atacicept, daratumumab)
- Agents targeted at reducing TNF (eg, infliximab, golimumab, certolizumab pegol, etanercept, CT-P13, and adalimumab)
- Interleukin-1 inhibitors (eg, canakinumab)
- Interleukin-2 inhibitors or exogenous IL-2 therapy
- Interferon inhibitors or exogenous IFN therapy
- IL-1 receptor antagonist (eg, anakinra)
- Any biologic targeting IL-6 or IL-6 receptor (eg, tocilizumab)
- Any janus kinase (JAK) inhibitor (eg, tofacitinib)
- Abatacept
- Anti-IL-17 agents (eg, brodalumab, secukinumab, and ixekizumab)
- Anti-IL-23 agents (eg, guselkumab and risankizumab)
- Leflunomide
- Intravenous or subcutaneous Ig
- Other immunomodulatory oral or topical preparations (eg, cyclosporine A and TAC) (see Section 6.5.4)
- Toll-like receptor inhibitors
- Thalidomide or lenalidomide
- Diaphenylsulfone
- ACTH by injection
- Epidural, IV, SC, IM, intra-articular, intrabursal, or intralesional administration of glucocorticoids

- Branched-chain amino acids

Cytotoxic drugs that are prohibited during the study include, but are not limited to, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.

The new use of drugs including but not limited to statins and fibrates that are known to cause drug-induced myopathy is discouraged.

The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited. In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

The use of other complementary therapies is strongly discouraged; in individual cases, use may be permitted following discussion with the sponsor.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

A participant's study drug must be discontinued if:

- The investigator and sponsor believe that for safety reasons or tolerability reasons (eg, AE) or due to severe, unstable, or rapidly progressive PM/DM disease activity it is in the best interest of the participant to discontinue the study drug.
- The participant becomes pregnant (Refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information).
- The participant experiences an AE temporally associated with the study drug infusion or injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure.
- The participant develops study drug hypersensitivity (eg, anaphylaxis, angioedema) reaction that is reported as serious or severe.
- The participant is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The participant develops new ILD or experiences clinically significant worsening of preexisting ILD during the study, confirmed by a pulmonologist based on HRCT findings and the investigator concludes that the study drug needs to be discontinued (See Section 8.2.5).
- The participant is deemed ineligible according to the following TB criteria:

  A diagnosis of active TB is made.

  A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.

A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive IGRA result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of the study drug and continued to completion. Indeterminate IGRA results should be handled as in Section 5.1. Participants with persistently indeterminate IGRA results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.

A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The participant develops a serious opportunistic infection.
- The participant requires high dose glucocorticoid (≥1 mg/kg/day of prednisolone or equivalent) for >2 weeks or a prohibited therapy such as a biologic, cyclophosphamide, or IV glucocorticoid (see Section 6.6).

  If a new immunomodulator or oral glucocorticoid (<1 mg/kg/day of prednisolone or equivalent) that is permitted per-protocol is initiated, then a participant will be considered a prohibited change in PM/DM medications but will not need to discontinue the study drug administrations. Addition of systemic medication for PM/DM activity must be discussed with the sponsor to determine the suitability of the participant to continue the study drug administrations.

If a participant discontinues the study drug for any reason on or before the Week 72 assessments should be obtained and scheduled assessments should be continued.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will not be automatically withdrawn from the study if he or she has to discontinue the study drug before the end of the study drug regimen.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Other

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. The study drug assigned to the withdrawn participant may not be assigned to another participant. Subjects who withdraw from the study will not be replaced. If a participant discontinues the study drug and withdraws from the study before Week 72, assessments should be obtained at a follow-up visit 8 weeks (EOT) and 16 weeks (EOS) after the last study drug administration. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. Due diligence should include repeated telephone calls, certified letters, and email requests. Measures taken to obtain follow-up information must be documented. Refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All patient-reported outcome (PRO) assessments, except for FI-2, should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO, electrocardiogram (ECG), vital signs, and blood

draw. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or participant or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The total blood volume to be collected from each participant will be approximately 750 mL.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Section 1.3, Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual and laboratory supplies
- Certain Clinical Outcome Assessments (COA; includes both PROs and Clinician Reported Outcomes [ClinROs])

  COA questionnaires and completion instructions
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Participant diary
- Any other manual or guideline that is deemed necessary for good execution of the study

8.1. Efficacy Assessments

8.1.1. Efficacy Evaluations

Every reasonable effort should be made to have all efficacy evaluations performed by the same study investigator or subinvestigator to achieve comparable measures over time.

8.1.1.1. Physician Global Activity

PhGA is a partially validated tool to measure the global evaluation by the treating physician of the overall disease activity of the patient at the time of assessment using a 10 cm VAS.[19] Visual analogue scale should be used for evaluation of IMACS TIS.

8.1.1.2. Patient Global Activity

PtGA is a partially validated tool to measure the global evaluation by the patient of the patient's overall disease activity at the time of assessment using a 10 cm VAS.[19]

8.1.1.3. Manual Muscle Testing

MMT is a partially validated tool to assess muscle strength.[19] 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.

8.1.1.4. Muscle Enzymes

Muscle enzymes are partially validated tool to measure the serum activities of muscle-associated enzymes including CK, the transaminases (ALT, AST), LDH, and aldolase.[19] The values obtained from central laboratory are used for evaluation. To calculate IMACS TIS, the most abnormal serum muscle enzyme level at baseline (CK, aldolase, ALT, AST, or LDH) will be used.

8.1.1.5. Extramuscular Assessment (Myositis Disease Activity Assessment Tool)

This validated tool measures the degree of disease activity of extramuscular organ systems and muscle.[19] This is a combined tool that includes the Myositis Disease Activity Assessment VAS (MYOACT), which is a series of physician's assessments of disease activity of various organ systems modified from the Vasculitis Activity Index,[29] and the Myositis Intention to Treat Activity Index (MITAX), which is modified from the British Isles Lupus Activity Group (BILAG) approach to assess disease activity in lupus.[7] The MITAX is composed of a series of organ-specific questions relating to the presence or absence of the clinical feature and the degree of treatment needed for it (intention to treat).

The MDAAT has undergone inter-rater reliability testing in adult myositis patients in workshops. 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. The tool is based on the results of clinical studies for reliability and validity. The current version is recommended for use in prospective trials

and clinical studies by IMACS. To calculate IMACS TIS, Extramuscular Global Assessment is used.

8.1.1.6. Physical Function (Health Assessment Questionnaire Disability Index)

The Stanford HAQ is a brief self-report questionnaire assessing physical function pertaining to activities of daily living in a variety of domains. Originally developed for use in RA, it has been successfully applied to a variety of rheumatic conditions, including idiopathic inflammatory myopathy. For IMACS TIS, the Disability Index is used, which is calculated by dividing the sum of the worst score of each section by the number of section tested.[19]

8.1.1.7. 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.[2]

8.1.1.8. 36-item Short Form

The SF-36 is a widely used tool to assess the global medical quality of life, functional health, and well-being of general and specific populations. It has shown evidence of content, concurrent, criterion, construct, and predictive validity in many different chronic diseases, and extensive normative data are available. It is also recommended by IMACS as an important measure to assess PROs in all forms of adult idiopathic inflammatory myopathy. It has a good construct and content validity in adult patients with DM, PM, or IBM.[19]

8.1.2. Endpoint Definitions

8.1.2.1. IMACS TIS

The IMACS response criteria are standardized clinical response criteria to assess minimal, moderate and major clinical improvement in patients with adult PM/DM, which was developed by IMACS.[1] These criteria, which have now been accepted by ACR and EULAR, are recommended for use as primary endpoints in myositis therapeutic trials. The criteria use the 6 IMACS core set measures, combining the absolute percentage change in each with varying weights to obtain a Total Improvement Score (TIS) on a scale of 0 to 100.

- PhGA
- PtGA
- MMT-8
- Muscle Enzymes
- Extramuscular Assessment (MDAAT)

- Physical Function (HAQ-DI)

Different thresholds of improvement have been set for minimal, moderate, and major response.

Minimal improvement is defined as IMACS TIS ≥20 in participants with PM/DM.

8.1.2.2. 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 PhGA 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

8.2. Safety Assessments

Safety evaluations will include assessment of AEs, concomitant medications, pregnancy testing (see Section 8.2.6), administration reactions, serum chemistry, hematology and blood coagulation laboratory tests, vital signs, ECG, general physical examinations, chest x-ray, HRCT, blood gas analysis, PFT, and TB testing. In addition, HIV, hepatitis B, hepatitis C will be required at screening (Section 1.3).

Details regarding the IDMC is provided in Committees Structure in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Section 1.3 Schedule of Activities:

8.2.1. Physical Examination

A physical examination will be performed pretreatment and during the study as shown in Section 1.3. A physical examination includes assessment of general appearance, head (including oral cavity and dentition), eyes, ears, nose, throat, neck, abdomen, lymph nodes, and peripheral

extremities and the following systems: cardiovascular (including peripheral vascular), respiratory, neurologic, musculoskeletal, skin, and genitourinary (if clinical history indicates need).

8.2.2. Vital Signs

Weight, temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiogram

A 12-lead ECG will be performed locally at screening. During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw. If an abnormal result is obtained, the ECG may be repeated.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, coagulation, and hematology will be collected as shown in Section 1.3 Schedule of Activities and Section 10.4, Appendix 4: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. With prior sponsor approval, local laboratories may be used in the event of a safety concern or if initiation of treatment is critical and the central laboratory results are not expected to be available before the need to provide study drug or take action to ensure participant safety.

8.2.5. Interstitial Lung Diseases and Respiratory Muscle

The presence of ILD and respiratory muscle weakness must be evaluated at screening using chest x-ray, chest HRCT, blood gas analysis (PaO_2 and partial pressure of carbon dioxide in arterial blood [$PaCO_2$]), and PFT (VC, FVC, DLCO, MIP, MEP, and/or MVV). All participants must be monitored with SpO_2, chest x-ray, laboratory data (KL-6 and SP-D), chest HRCT, and PFT as scheduled in Section 1.3 during the study. The investigator may consider additional examination including C-reactive protein, ferritin, and blood gas analysis as needed. In case of worsening or new onset of lung lesion, it is recommended to make a differential diagnosis of fungal infection, cytomegalovirus infection, heart failure and/or other cause using additional laboratory data such as β-D-glucan, C7-HRP, and/or BNP. If the investigator identifies new onset or worsening of ILD or observes any finding which needs to be evaluated by a pulmonologist, the investigator should consider consultation with a pulmonologist and administer rescue treatment as needed. Permanent discontinuation of the study drug must be considered for participants who experience worsening of ILD or newly identified severe ILD that is considered serious or severe by the investigator in cases of the following but not limited to;

- Significant worsening of ILD findings based on chest x-ray or HRCT
- Significant decrease in SpO_2 such as $SpO_2 < 90\%$ or a decrease of SpO_2 by 5% or more

The result of consultation with a pulmonologist and the decision by the investigator should be recorded and discussed with the sponsor.

In addition, IDMC will monitor the safety data including ILD evaluation mentioned above. If IDMC identify any safety concern, IDMC will recommend the investigator withdrawal of the study drug as needed.

8.2.6. Pregnancy

Female participants of childbearing potential are to be monitored for possible pregnancy using a urine dipstick test performed at the clinical site as shown in Section 1.3. Additional serum hCG testing may also be performed locally or at the central laboratory if desired by the study investigator.

Pregnancies (of the study participant or if the participant is male, then the participant's partner) must be followed to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study early.

8.2.7. Infections

Participants will be counseled on the signs and symptoms of infections and will be instructed to contact the site between scheduled visits should any signs and symptoms occur. At each site visit, investigators or other site personnel are required to evaluate participants for any signs or symptoms of infection and ask about symptoms of infection or other AEs that may have occurred between site visits. Investigators need to consider additional laboratory examination (such as test for fungal or viral antigen) based on each participant’s risk of opportunistic infection.

8.2.7.1. Tuberculosis

In addition to general evaluation for infection, monitoring for TB will be performed with chest x-ray or chest HRCT and IGRAs as scheduled in Section 1.3.

8.2.8. Infusion- or Injection-site Reactions

Participants should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, or surrogate,) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator within 16 weeks after the last dose of the study drug or completion of the participant's last study-related procedure, whichever comes later, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are events which are noted by participants in their participant diary (see Section 8, Study Assessments and Procedures).

Unsolicited Adverse Events

Unsolicited AEs are all AEs other than solicited AEs as defined above.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Refer to Section 10.6, Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting for details for which a medical device is provided for use in the study.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For individual SAEs, the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study drug.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Infections

The study drug should not be administered to a participant with a clinically important, active infection. Treatment with the study drug should be withheld until serious and/or severe infections are completely resolved. If a participant develops a serious or severe infection, including but not limited to sepsis or pneumonia, discontinuation of the study drug must be considered. Treatment must be permanently discontinued for participants who develop a serious opportunistic infection. This should be discussed with the sponsor. For active varicella zoster infection or a significant exposure to varicella zoster infection in a participant without history of chickenpox, the participant should be evaluated for symptoms of infection and if the participant has received appropriate treatment and/or recovered or has no symptoms of infection, he/she may continue the study drug after discussion with the sponsor.

8.3.6.1. Tuberculosis

Any newly identified case of active TB occurring after the first administration of the study drug in participants participating in this clinical study must be reported by the investigator according to

the local procedures. These events are to be considered serious only if they meet the definition of an SAE. Treatment must be permanently discontinued for participants with active TB.

8.3.7. Infusion- or Injection-site Reactions

An infusion reaction is defined as an AE that occurs during or within 1 hour following the infusion of the study drug, excluding laboratory abnormalities. Permanent discontinuation of the study drug must be considered for participants who experience an AE of infusion reaction that is considered serious or severe by the investigator.

8.4. Events of Special Interest

Adverse events of special interest: 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 occurring after the first administration of study agent in participants in this clinical study must be reported by the investigator following procedures. Investigators are also advised that active TB is considered a reportable disease required by local regulations. These events are to be considered serious only if they meet the definition of an SAE as shown in Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5. Treatment of Overdose

For this study, any dose of ustekinumab greater than set daily dose at Section 6.1 within 2 weeks time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the sponsor immediately.
- Closely monitor the participant for AE/SAE, laboratory abnormalities, and any signs or symptoms until ustekinumab can no longer be detected systemically (at least 16 weeks).
- Appropriate symptomatic treatment be instituted immediately.
- Obtain a serum sample for PK analysis if requested by the sponsor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics and Immunogenicity

Serum samples will be collected for measurement of serum concentrations of ustekinumab and presence of anti-ustekinumab antibodies. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.6.1. Evaluations

The total blood volume to be collected from each participant will be approximately 750 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.6.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

Immunogenicity

The detection and characterization of anti-ustekinumab antibodies will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of anti-ustekinumab antibodies will also be evaluated for ustekinumab serum concentration to enable interpretation of the antibody data.

8.6.3. Pharmacokinetic Parameters and Evaluations

Based on the individual serum concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of ustekinumab may be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

8.6.4. Immunogenicity Assessments (Anti-ustekinumab Antibodies)

Anti-ustekinumab antibodies will be evaluated in serum samples collected from all participants according to the Time and Events Schedule (See Section 1.3, Schedule of Activities). Additionally, serum samples should also be collected at the final visit from participants who are discontinued from intervention or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. The detection and characterization of anti-ustekinumab antibodies will be performed using a validated assay method by or under the supervision of the sponsor.

Serum samples will be screened for antibodies binding to ustekinumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ustekinumab. Serum samples that test positive for anti-ustekinumab antibodies will be further characterized to determine if anti-ustekinumab antibodies could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies [NAbs] to ustekinumab). All samples will be tested by the sponsor or sponsor's designee.

8.7. Genetics

A pharmacogenomic blood sample (whole blood DNA) will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

DNA samples will be analyzed for identification of genetic factors to better understand the molecular effects of ustekinumab and/or susceptibility to PM/DM, and to evaluate markers that can predict clinical response. Such analysis may include the human leukocyte antigen (HLA) alleles and any relevant single nucleotide polymorphisms that are reported to be associated with ustekinumab and/or the development of PM/DM.

8.8. Biomarkers

Whole blood will be prospectively collected, processed and cryopreserved appropriately for immune and other biomarker evaluations.

Biomarker assessments may include but not limited to immunophenotyping (by flow cytometry and/or cytometry by time-of-flight [CyTOF]), gene expression (RNA) as well as disease related soluble autoantibody profiles, markers of inflammation and other biomarkers associated with IL12/IL23 pathway. Assessments will be performed to identify biomarkers that are relevant to ustekinumab treatment.

Serum samples for autoantibody and soluble proteins profiling

Serum samples may be used to detect circulating autoantibodies associated with PM/DM (such as anti-aminoacyl-tRNA synthetases [Jo-1, PL-7, PL-12, EJ, OJ, KS], anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR, etc). In addition, soluble levels of Type I, II and III IFN may be quantitated. Furthermore, biomarkers associated with inflammation, tissue injury and other soluble proteins may be measured using relevant technological platforms. Immunoglobulin isotypes may be characterized.

Whole blood and/or PBMC samples for immune profiling

Assessment of immune profiling biomarkers including phenotypic and functional assessments are anticipated to be performed as outlined below pending availability of samples and validated assays:

Flow cytometry and /or CyTOF assessments including but not limited to T cell, B cell, Dendritic cell, natural killer cell subsets may be performed.

In vitro functional assays to monitor immune cell responses to relevant stimulations and single cell analysis of immune populations may be performed.

Whole blood RNA for gene expression analyses

Whole blood collected for RNA may be used in the expression analysis of broader gene transcripts and/or targeted genes indicated in the IFN or cytotoxic pathway signatures. Technological platforms may include microarray, RNASeq or relevant targeted gene analysis platforms.

In addition, sequencing of T cell and B cell receptor genes using whole blood RNA may be conducted to better understand the repertoire composition, clonal diversity and sequence abundance.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Descriptive statistics (eg, mean, median, standard deviation [SD], interquartile range, minimum, maximum) will be used to summarize continuous variables. Numbers and percentages will be used to summarize categorical variables. Median values will be reported for time-to-event variables. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

Simple descriptive summary statistics, such as sample size (n), mean, SD, median, interquartile (IQ) range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of participants achieving endpoints (eg, IMACS TIS response). In cases of rare events, the Fisher exact test will be used for treatment comparisons. For continuous efficacy endpoints, treatment comparisons will be performed using either a mixed-effect model repeated measure (MMRM) model especially with longitudinal data or an analysis of covariance (ANCOVA) model. If the normality assumption is in question, an analysis of variance (ANOVA) or ANCOVA on the van der Waerden normal scores will be used. Time-to-event endpoints will be analyzed using a log-rank test and Kaplan-Meier plots and adjusting for potential confounders will be performed using a Cox proportional hazards model. All the models will have treatment group, the adjusting for baseline stratifications as appropriate, and may include baseline value as covariate.

In general, all statistical tests will be performed at a 2-sided significance level of α 0.05. Nominal p-value will be displayed for all treatment comparisons.

9.1. Statistical Hypotheses

This study is designed to show that treatment effect (as measured by the IMACS TIS response at Week 24) of an 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:

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

Superiority can be concluded if the 2-sided p-value adjusted by the stratification factors for the testing of the hypothesis above is less than 0.05.

9.2. Sample Size Determination

The sample size calculation is based upon the primary endpoint, the proportion of participants who achieve IMACS TIS response at Week 24. Some published studies designed to assess the efficacy

of biological therapies in active PM/DM patients using International Myositis Assessment and Clinical Studies Definition of Improvement (IMACS DOI) indicated a clinically relevant response following the use of biological therapies in the PM/DM population (Table 3). However, since ustekinumab is not previously evaluated in any studies for the treatment of patients with active PM/DM, its effectiveness in this population evaluated by IMACS DOI (IMACS TIS) is not well understood. To determine the effect size versus placebo used for calculating the sample size, meta-analyses were conducted for the synthesis of the evidence (Table 4 and Table 5).

By reviewing the literature search results on PubMed and publications listed on the IMACS academic web site, the following 4 articles were selected to be included in the meta-analyses.

Table 3: Overview of IMACS DOI Response Rates at Week 24 in Selected Studies

Reference	Placebo group	Active group
The Muscle Study Group[15]	40.0% (2/5)	81.8% (9/11)
Oddis et al, 2013[16]	---	82.6% (161/195)[a]
Zong et al, 2014[32]	---	50.0% (5/10)
Tjarnlund et al, 2018[24]	11.1% (1/9)	60.0% (6/10)

Key: IMACS DOI=International Myositis Assessment and Clinical Studies Definition of Improvement
[a] This response was observed at Week 44

Due to the disproportionately large number of patients and the evaluation timepoint difference in the study by Oddis et al, 2013,[16] meta-analyses using random-effect, fixed-effect, and Bayesian models were conducted separately for deletion and inclusion of this study from the pool of the above 4 studies.

Table 4: Meta-analysis Using Random-effect and Fixed-effect Models: Pooled IMACS DOI Response Rates at Week 24 and Their 95% CIs

Model	Inclusion/Exclusion of Studies	Group	Mean (95% CI)
Fixed-effect[3]	Excluding Oddis et al, 2013[16]	Placebo	0.17 (0.00, 0.35)
		Active	0.68 (0.52, 0.84)
	Including Oddis et al, 2013[16]	Placebo	0.17 (0.00, 0.35)
		Active	0.81 (0.76, 0.86)
Random-effect[3]	Excluding Oddis et al, 2013[16]	Placebo	0.19 (0.00, 0.45)
		Active	0.66 (0.47, 0.86)
	Including Oddis et al, 2013[16]	Placebo	0.19 (0.00, 0.45)
		Active	0.74 (0.60, 0.88)

Key: CI=confidence interval; IMACS DOI=International Myositis Assessment and Clinical Studies Definition of Improvement

Table 5: Meta-analysis Using Bayesian Model With Non-informative Prior: Posterior Summary of IMACS DOI Response Rates at Week 24

Inclusion/Exclusion of Studies	Group	2.5 percentile	Median	97.5 percentile
Excluding Oddis et al, 2013[16]	Placebo	0.07	0.25	0.51
	Active	0.47	0.61	0.77
Including Oddis et al, 2013[16]	Placebo	0.07	0.25	0.51
	Active	0.75	0.80	0.85

Key: IMACS DOI=International Myositis Assessment and Clinical Studies Definition of Improvement

A few recent ustekinumab clinical trials reported the dropout rates varied from 7.5% to 18.6% in overall population and the dropout rates varied from 7.5% to 9.5% in Japanese population, through 44 or 52 weeks (Table 6). Considering the primary endpoint evaluated at Week 24 in Japanese patients, a dropout rate of 5% is accommodated for sample size calculation.

Table 6: Overview of the Drop-out Rates in a Few Recent Ustekinumab Clinical Trials

Study or reference	Population	Follow-up period	Drop-out rate	
			Overall population	Japanese population
CNTO1275SLE2001	SLE	44 weeks	18.6% (19/102)	---
CNTO1275CRD3003	CD	44 weeks	9.1% (36/397)	9.5% (2/21)
Igarashi 2012[8]	PSO	52 weeks	7.5% (12/160)	7.5% (12/160)

Key: CD: Crohn's disease; PSO: Psoriasis; SLE: Systemic lupus erythematosus.

Based on the above data, assuming a response rate in placebo ranged from 15% to 30%, a response rate in ustekinumab ranged from 50% to 75% and a dropout rate of 5%, the power to detect a significant treatment difference at α 0.05 (2-sided) with a fixed sample size of 50 participants is estimated by the simulation. The results are shown in Table 7.

Table 7: Power for a Fixed Sample Size (50 Participants in Total) at Alpha=0.05 (2-sided) to Detect a Significant Treatment Difference in the Proportion of Participants With IMACS TIS Response at Week 24 Assuming a Drop-out Rate of 5%

Assumed response rate (%)		Absolute increase in response (%)	Odds ratio	Power (%)
Placebo group	Ustekinumab group			
15	50	35	5.67	76.0%
	55	40	6.93	85.3%
	60	45	8.50	91.8%
20	55	35	4.89	73.3%
	60	40	6.00	82.5%
	65	45	7.43	90.8%
25	60	35	4.50	71.8%
	65	40	5.57	82.2%
	70	45	7.00	90.3%
30	65	35	4.33	71.4%
	70	40	5.44	82.9%
	75	45	7.00	90.4%

Key: IMACS TIS International Myositis Assessment and Clinical Studies Total Improvement Score

Particularly focusing on the effect size of 40% which is considered a reasonable estimate of effect size based on the above meta-analyses results, 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 in response over placebo or an odds ratio of 5.57) with an alpha level of 0.05 (2-sided).

9.3. Populations for Analyses

- The primary efficacy analysis set will be based upon the intention-to-treat (ITT), namely, defined as randomized participants. The primary efficacy analysis set will be analyzed based on assigned treatment groups, regardless of the treatment receive.

- The safety analysis set will include all randomized participants who receive at least 1 dose (partial or complete) of ustekinumab and participants will be analyzed based on the treatment they receive, regardless of the treatment groups to which they are assigned.
- The PK analysis set will include all participants who receive at least 1 complete dose of ustekinumab and have at least 1 postdose sample collection.
- The immunogenicity analysis set is defined as all participants who receive at least 1 dose (partial or complete) of ustekinumab and have at least 1 postdose sample collection. Participants will be analyzed according to the actual treatment receive.
- The pharmacodynamic (PD) analysis set is defined as all participants who receive at least 1 dose (complete or partial) ustekinumab. Participants will be analyzed according to the actual treatment receive.

For all participants who are randomly assigned to study drug, descriptive statistics (eg, study completion/withdrawal information, demographic and baseline data) will be provided.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

It is considered that the effectiveness of ustekinumab treatment in adult patients with PM/DM will be demonstrated if the ustekinumab group is shown to be superior to placebo group for the primary efficacy analysis in this study.

9.4.1.1. Primary Endpoint Analysis

The primary endpoint of this study is the proportion of participants who achieve IMACS TIS response at Week 24 (Section 8.1.2.1).

9.4.1.1.1. 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. 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.
- **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. The prohibited changes in PM/DM medications will be defined in the SAP.

Participants with intercurrent events (ICEs) 1-2 before Week 24 will be considered as non-responders at Week 24. 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. How the remaining missing data are treated after accounting for the ICEs will be specified in the SAP.

In the primary efficacy analysis, data from all randomized participants will be analyzed according to their assigned treatment group regardless of their actual treatment received.

Logistic regression adjusting for 2 stratification factors, 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 and the 95% confidence interval (CI) will be provided.

9.4.1.1.2. Estimands other than the primary estimand

Additional sensitivity/supplemental analyses which vary how intercurrent events (eg, supplemental estimand) are handled, how observed data are used, and how missing data are treated will be specified in the SAP to further address the robustness of the primary estimand.

9.4.1.1.3. Subgroup Analyses

Subgroup analysis of the primary endpoint based on stratification factors will be performed. Subgroup analysis of the primary endpoint by other selected baseline characteristics may be also presented and will be defined in SAP:

- Disease subset (PM/DM)
- Baseline treatment level (glucocorticoid dose [≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent])

For subgroup analyses, proportion of IMACS TIS response in each treatment group and corresponding 95% CI will be presented. However, p-values for the comparison across treatment groups for the subgroups will not be presented.

9.4.1.2. Secondary Efficacy Analyses

All endpoints other than the primary endpoint of this study are not prospectively powered. P-values will be provided without adjusting multiplicity for secondary endpoints analyses.

- Treatment comparison in time to worsening through Week 24 will be done using a log-rank test. Kaplan-Meier estimates will be provided for each treatment group. Analysis for time to worsening will be repeated adjusting for 2 stratification factors using a proportional hazards model. In the analyses for time-to-event endpoints, subjects with ICE 1-2 will be handled with **Composite Strategy** and subjects with ICE 3 will be handled with **Treatment Policy Strategy** (the observed data will be used regardless of whether or not this ICE had occurred)**.**
- Analyses comparing the 2 treatment arms will be performed using a logistic model similar to primary analysis with the binary outcome related to individual core set measures at Week 24. The primary estimand approaches dealing with ICEs will be applied to these analyses.
- All other efficacy endpoints will be summarized over time by treatment group. Treatment comparisons will be performed using an MMRM model where there are repeated continuous measurements or a logistic model where there is a dichotomous response variable. The primary estimand approaches dealing with ICEs will be applied to these analyses also and the detailed methods of analysis and the data-handling rules will be provided in the SAP.

9.4.2. Safety Analyses

Routine safety evaluations will be performed. Adverse events, SAEs, reasonably related AEs, and AEs by severity will be summarized by treatment group. More specification of other special interesting events such as malignancies, serious infections, serious cardiovascular events, and ILD will be described in the SAP. However, a summary table will not be provided if the number of events is too few to provide meaningful summary.

The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of participants with abnormal laboratory parameters (hematology and chemistry) based on NCI-CTCAE toxicity grading will be summarized by treatment group. Listings of SAEs will also be provided. All safety analyses will be based on the population of participants who receive at least 1 dose of either study drug; participants will be summarized by the treatment they receive.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

AEs of COVID-19, if any occurs, will be summarized separately from other AEs.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the changes from baseline will be presented in pre- versus postintervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

Clinically relevant abnormalities will be evaluated by frequency tabulations.

Vital Signs

Descriptive statistics of weight, temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized over time. Descriptive statistics, including arithmetic mean, SD, median, IQ range, minimum, and maximum will be calculated at each sampling time point. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

If feasible, population PK analysis of ustekinumab will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Biomarkers Analyses

Biomarker analyses performed may include but not limited to serum analysis for levels of IFN as well as molecular pathway profiling for evidence of IL-12 and IL-23 pathway modulation. The biomarkers analyzed may include inflammatory markers, RNA, autoantibodies, T, B, and natural killer (NK) cell immunophenotyping, and other categories of biomarkers potentially involved in the development and the progression of PM/DM.

Analytes may include (but are not limited to):

- Ig isotype profile (IgG, IgM, IgA levels)
- IL-12/IL-17/IL-23 (eg, mRNA, Soluble Protein [Serum])
- Anti-aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS)
- Anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR
- Type I, II, and III IFNs
- Other inflammation-related molecules and autoantibody profile
- Participant whole blood gene expression

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.

Immunogenicity Analyses

The incidence of anti-ustekinumab antibodies and the impact of antibodies on serum ustekinumab concentrations will be summarized.

A listing of participants who are positive for antibodies to ustekinumab will be provided. The maximum titers of antibodies to ustekinumab will be summarized for participants who are positive for antibodies to ustekinumab.

The incidence of NAbs to ustekinumab will be summarized for participants who are positive for antibodies to ustekinumab and have samples evaluable for NAbs to ustekinumab.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum ustekinumab concentration and efficacy measures for primary and selected key secondary endpoints will be analyzed graphically. In addition, population PK/PD modeling may be performed to characterize the relationship between serum ustekinumab exposure and efficacy measures. Further details will be provided in a population PK/PD analysis plan and the results will be provided in a separate report.

9.5. Interim Analysis

A futility analysis based on the primary endpoint of IMACS TIS at Week 24 will be conducted when 20 participants (40% of the originally planned total sample size) have completed the Week 24 visit. This futility analysis is non-binding. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) is less than a prespecified cutoff. The prespecified cutoff value will be 0.20. For the futility analysis, the treatment assignment information will be unblinded to IDMC and independent statistical support group (SSG) for the 20 participants included in the interim analysis only (the treatment assignment for the remaining participants will remain blinded at this time). The details will be stated in interim analysis charter. To protect the integrity of the study, the unblinding of the treatment assignments and this futility analysis will be handled by an external IDMC and an independent SSG that are organized outside of the sponsor. The SSG will perform the interim analysis and the IDMC will form a recommendation on whether or not to stop the trial for futility. The sponsor decision committee will then review the IDMC's recommendation and make a final decision.

The conditional power is estimated by the method proposed by Proschan.[18] The simulation study demonstrates that this futility analysis will result in a slight loss in power (≤0.6%) when the treatment effect is expected to be 40% assuming the response rate in the placebo group as 25% and Type I error rate will not inflate (α 0.05, 2-sided) for the primary endpoint analysis. Details about the futility analysis will be specified in the interim analysis plan before the time at which the futility analysis is performed.

The SAP will describe the planned interim analysis in greater detail.

9.5.1. Independent Data Monitoring Committee

An IDMC will be established as noted in Committees Structure in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to meet interim analysis objectives. The committee will meet to review the safety and interim data. After the review, the

IDMC will make recommendations to the Sponsor Committee who is separate from the study team regarding the continuation of the study. The details will be provided in a separate IDMC charter. As needed basis, the IDMC might ask the study team to provide with further information via the IDMC bureau. The study team make the best effort to collect the further information from each investigational site for the evaluation by the IDMC.

The IDMC will consist of 2 medical experts in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

The study team is defined as a cross-functional team responsible for the planning, initiation, execution, analysis, and reporting of a trial. This may include but is not limited to: Study Responsible Physician/Scientist, Global Data Manager, Global Trial Manager, Central Monitoring Manager, Site Manager, Local Trial Manager, Study Programmer, Study Statistician, Quality Monitoring & Compliance representative, Clinical Pharmacology representative, and Patient Reported Outcomes Group Leader.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADM	amyopathic dermatomyositis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc total	HBV core antibody total
anti-HBs	HBV surface antibody
AST	aspartate aminotransferase
AZA	azathioprine
BQL	below the lowest quantifiable sample concentration of the assay
CD	cluster of differentiation
CIM	C protein-induced myositis
CK	creatine kinase
COA	clinical outcome assessment (paper or electronic)
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DC	dendritic cells
DLCO	diffusing capacity of the lungs for carbon monoxide
DM	dermatomyositis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report forms
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EULAR	European League Against Rheumatism
FI-2	Functional Index-2
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high-resolution computer tomography
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBM	inclusion body myositis
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IGRA	interferon gamma release assay
IIM	idiopathic inflammatory myositis
IL	interleukin
ILD	interstitial lung disease
IM	intramuscular
IMACS DOI	International Myositis Assessment and Clinical Studies Definition of Improvement
IMACS TIS	International Myositis Assessment and Clinical Studies Total Improvement Score
IQ	interquartile

IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
MDAAT	Myositis Disease Activity Assessment Tool
MEP	maximal expiratory pressure
MHC	major histocompatibility complex
MIP	maximal inspiratory pressure
MITAX	Myositis Intention to Treat Activity Index
MMF	mycophenolate mofetil
MMRM	mixed-effect model repeated measure
MMT	Manual Muscle Testing
mRNA	messenger RNA
MTX	methotrexate
MVV	maximal voluntary ventilation
NAbs	neutralizing antibodies
NCI	National Cancer Institute
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PFS	prefilled syringe
PFT	pulmonary function test
PK	pharmacokinetic
PM	polymyositis
PQC	product quality complaint
PRO	patient-reported outcome
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	36-item short form
SI	International System of Units
SLE	systemic lupus erythematosus
SSG	statistical support group
SUSAR	suspected unexpected serious adverse reactions
TAC	tacrolimus
TB	tuberculosis
Tfh	T follicular helper
TNF	tumor necrosis factor alpha
tRNA	transfer RNA
ULN	upper limit of normal
VAS	Visual Analogue Scale
VC	vital capacity
WBC	white blood cell

Definitions of Terms

Clinical outcome assessment (COA)	Includes PROs, Clinician Reported Outcomes (ClinROs), Observer Reported Outcomes (ObsRO) and Performance Reported Outcomes (PerfRO)
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the 'Protocol Supplementary Information', which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of the study drug to the study site:

- Protocol signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion, the notification will be submitted through the head of investigational institution.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICFs must be signed before performance of any study-related activity. The ICFs that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research. After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

A separate ICF may be used for the required DNA component of the study.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory (DNA, PD, biomarker, PK, and immunogenicity) research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore,

exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand PM/DM, to understand differential intervention responders, and to develop tests/assays related to ustekinumab and PM/DM. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to meet interim analysis objectives. This committee will consist of 2 medical experts in the relevant therapeutic area and at least 1 statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review the safety and interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ustekinumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the

study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study

completion and reason for early discontinuation of the study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Investigator-completed scales and PRO assessments

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the

sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the

responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study drug development

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as

a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an AE will be determined by whether or not it is listed in the IB.[9] For standard-of-care background therapies with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the intervention.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number

- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study within 16 weeks of the last dose of the study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the 'Protocol Supplementary Information', which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality,

durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the 'Protocol Supplementary Information', which will be provided as a separate document.

10.4. Appendix 4: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell count (RBC) RBC morphology Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Nonfasting Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Aldolase FSH as needed	Alkaline phosphatase Creatine kinase (CK) Lactic acid dehydrogenase (LDH) Calcium Phosphorous Albumin Total protein Krebs von den Lungen-6 (KL-6) surfactant protein-D (SP-D) total bilirubin, and if total bilirubin is abnormally elevated, then direct bilirubin and indirect bilirubin
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein (eg, myoglobin) Blood Ketones Bilirubin Urobilinogen	Sediment microscopy (if dipstick result is abnormal) RBC WBC Epithelial cells Crystals RBC, WBC, or heme-granular Casts Bacteria
	If dipstick result is abnormal, microscopy will be used to measure sediment. In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory. Dipstick and sediment analysis of the urine samples will be performed in parallel at screening, ie, in the same sample at the same time. Specific gravity, pH, glucose, protein (eg, myoglobin), blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBC, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry or microscopy. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Crystals, casts, and bacteria will only be reported if they are present.	

Laboratory Assessments	Parameters
Coagulation	• Prothrombin Time • activated Partial Thromboplastin Time (aPTT) • International Normalized Ratio (INR)
Biomarkers	• Ig isotype profile (IgG, IgM, IgA levels) • IL-12/IL-17/IL-22/IL-23 (eg, mRNA, Soluble Protein [Serum]) • Anti-aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS) • Anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR • Type I, II, and III IFNs • Other inflammation-related molecules and autoantibody profile
Other Screening Tests	• Urine pregnancy testing for women of childbearing potential only (performed locally) • Serum pregnancy test (at the discretion of the investigator) • Viral serology (HIV antibody, HBsAg, anti-HBs, anti-HBc total, and HCV antibody) • IGRA (performed locally) • anti-TIF1-γ (performed locally) • anti-MDA5 (can be performed locally)

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.2.6, Pregnancy and Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **Premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **Postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use 1 of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **Permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)

• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, postovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

See Section 8.3.5.

10.6. Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1, Study Interventions Administered for the list of sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the eCRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate Adverse Event/Serious Adverse Event eCRF page will be completed as described in Section 10.3,

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

- The eCRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

10.7. Appendix 7: Cancer Screening Test

The following tests will be performed according to the Schedule of Activities:

Protocol-required Cancer Screening Tests

Cancer	Assessments for screening*	Age	Sex
Gastric cancer	Medical interview and Gastric x-ray or Gastroendoscopy	≥50	Male and Female
Cervical cancer	Medical interview, Inspection and Cytological diagnosis and Pelvic examination in the cervix	≥20	Female
Lung cancer	Medical interview, Chest x-ray and Sputum cytology**	≥40	Male and Female
Breast cancer	Medical interview and Mammography	≥40	Female
Colon cancer	Medical interview and Stool test for occult blood	≥40	Male and Female

* Assessments can be replaced by alternative tests which have equivalent or better sensitivity and specificity (eg, colonoscopy for colon cancer).
** This cytology is needed for participants are ≥50 years old and meet smoking index (number of cigarettes smoked per day x years) is ≥ 600.

Participants should be performed cancer screening tests dependent on the status of anti-TIF1-γ antibody as follows;

a. If participants have negative test result for anti-TIF1-γ antibody, these cancer screening tests should be tested according to the age at informed consent and sex of participants.
b. If participants have positive test result for anti-TIF1-γ antibody, these cancer screening tests should be tested irrespective of age according the sex of participants.

The investigator should confirm the results of cancer screening tests brought by participants if they were performed at any other sites within 2 years.

10.8. Appendix 8: Hepatitis B Virus Screening

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.

Participants who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this study, regardless of the results of other hepatitis B tests.

Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and/or*** surface antibody (anti-HBs+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the patient ***is not eligible*** for this study. If the HBV DNA test is **negative**, the patient ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the patient ***is not eligible*** for this study. If core antibody (anti-HBc) and/or surface antibody (anti-HBs) are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

Eligibility based on Hepatitis B virus test results				
	Hepatitis B test result			
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**Hepatitis B viral DNA (HBV DNA) ***
Exclude	+	— *or* +	— *or* +	NA
	—	—	+	+
	—	+	—	+
	—	+	+	+
Include	—	—	—	NA
	—	—	+	—
	—	+	—	—
	—	+	+	—
* If HBV DNA is detectable, exclude from clinical trial. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from clinical trial.				

Reference;

Japan College of Rheumatology: Recommendations on Immunosuppressive Therapy in Patients with Rheumatic Disease and Hepatitis B Virus Infection, Revised Version; Oct. 18. 2011.

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2 (4 Jun 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to implement clarifications to the protocol as well feedback from key opinion leaders and study investigators.

Section number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	n. In addition to the urine screening evaluation, a serum pregnancy test may be conducted at any time at the discretion of Investigator or participant. Urine pregnancy tests may be conducted more frequently (eg, monthly basis). Urine pregnancy tests may not be necessary if a subject is considered a postmenopausal state defined as no menses for 12 months without an alternative medical cause and a high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) during the study.	Text was added to clarify the condition of participants who may not be required urine pregnancy tests.
5.1. Inclusion Criteria 12.	Criterion modified per Amendment 2: 12.1 Must be receiving 1 or more of the following protocol-permitted, systemic standard-of-care treatments: •If using 1 or 2 of the following immunomodulatory drugs within the range of maximum dose or concentration, must be receiving all of those for ≥8 weeks and be on a stable dose for ≥4 weeks prior to first dose of the study drug: – MMF ≤3 g/day – AZA 1 to 2 mg/kg/day; up to 3 mg/kg/day – Oral MTX ≤15 mg/week with concomitant folic acid or calcium folinate – Oral TAC targeting~~at~~ trough concentration of 5 to 10 ng/mL – Oral cyclosporine A targeting~~at~~ trough concentration of 100 to 150 ng/mL	Text was revised to clarify the inclusion criteria for the standard of treatment based on the local guideline and the package insert.
6.5.3. Non-biologic Immunomodulators	Participants are allowed to use up to ~~1~~ 2 of the following immunomodulatory drugs without any change in dose from baseline (Week 0) through Week 24.	

Section number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria 13.	Criterion modified per Amendment 2: 13.1 Regular or as needed treatment with topical use of ~~medium/mild (Group IV) or weak (Group V) potency~~ glucocorticoids are permitted to treat skin lesions ~~of DM~~ on a stable dose for ≥2 weeks prior to first dose of the study drug. (see Section 6.5.4. for potency of topical glucocorticoids)	Text was revised to clarify the permitted usage of topical medications as well as the medical conditions, for which topical medications can be permitted
6.5.4. Topical Medications	For the treatment of cutaneous lesion in participants with PM/DM or other concurrent medical conditions, regular use of topical medications is permitted. However, topical compounds cannot include a prohibited medication. Topical glucocorticoids must be medium/mild (Group IV) or weak (Group V) potency glucocorticoids to treat cutaneous lesions of myositis or skin disease of the same area as cutaneous lesions of myositis. Topical glucocorticoids may be very strong (Group II) or weaker potency glucocorticoids to treat cutaneous lesions of other concurrent medical conditions whose area is different from cutaneous lesions of myositis. "As needed" use of topical ~~medium/mild (Group IV) or weak (Group V) potency~~ glucocorticoids is permitted, but not within 48 hours prior to a study visit for efficacy assessment. The investigator should notify the sponsor if~~After discussion with the sponsor,~~ topical glucocorticoids of very strong (Group II~~I~~) or weaker potency are~~may be~~ used on skin lesion up to 2 weeks where there is no preexisting skin eruptions of myositis ~~DM~~ in case it is considered due to adverse events other than cutaneous lesions of myositis ~~DM~~.	
5.4. Screen Failures Rescreening	If a participant is a screen failure, the participant may be rescreened 1 additional time after a period of at least 30 days. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process again, and restart a new screening phase with carrying screening test results over from previous screening if appropriate.	Text was added to clarify the procedure of rescreening.
6.5.2. Glucocorticoid Therapy	Glucocorticoid dose needs to be reduced based on the table of glucocorticoid tapering schedule (See Table 2). Reduction of glucocorticoid dose should follow study drug administration at the weeks of study drug administration.	Text was added to clarify the procedure of reduction of glucocorticoid dose.
6.6. Prohibited Therapies	• Intravenous or subcutaneous Ig	Text was revised to clarify the details of immunoglobulin in

Section number and Name	Description of Change	Brief Rationale
		prohibited therapies.
7.1. Discontinuation of Study Drug	Addition of ~~new therapy~~systemic medication for PM/DM activity must be discussed with the sponsor to determine the suitability of the participant to continue the study drug administrations.	Text was revised to clarify Discontinuation of Study Drug
10.4. Appendix 4: Clinical Laboratory Tests	**Laboratory Assessments** / **Parameters** Hematology: platelet count; Red blood cell count (RBC); RBC morphology; Hemoglobin; Hematocrit ~~Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.~~ Other Screening Tests: • Urine pregnancy testing for women of childbearing potential only (performed locally); • Serum pregnancy test (at the discretion of the investigator); • Viral serology (HIV antibody, HBsAg, anti HBs, anti HBc total, and HCV antibody); • IGRA (performed locally); • anti TIF1 γ(performed locally); • anti MDA5 (can be performed locally)	Text was revised to clarify the parameters and note of Clinical Laboratory Tests.
10.7. Appendix 7: Cancer Screening Test	~~10.8.~~10.7. Appendix ~~7~~8: Cancer Screening Test **Cancer** / **Assessments for screening*** / **Age** / **Sex** Lung cancer / Medical interview, Chest x ray and Sputum cytology** / ≥40 / Male and Female * Assessments can be replaced by alternative tests which have equivalent or better sensitivity and specificity (eg, colonoscopy for colon cancer). ** This cytology is needed for participants are ≥50 years old and meet smoking index (number of cigarettes smoked per day x years) is ≥ 600.	Text was added to clarify the alternative tests for cancer screening test based on medical practice in Japan.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (13 August 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is to implement clarifications to the protocol as well feedback from key opinion leaders and study investigators.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis Secondary Endpoints Tertiary Endpoints 1.3.Schedule of Activities (SoA) Time and Events Schedule 3. OBJECTIVES AND ENDPOINTS ENDPOINTS Secondary Endpoints Tertiary Endpoints 5.1.Inclusion Criteria 10. 8.1.1.1. Physician Global Activity 8.1.2.1. IMACS TIS 8.1.2.2.Disease Worsening 9.4.1.1.2.Treatment Failure Criteria	Mean change from baseline in Physician Global Activity (PhGA) ~~Visual Analogue Scale (VAS)~~ at Week 24 Mean change from baseline in ~~Physician Global Activity~~ PhGA ~~VAS~~ over time The proportion of participants with improvement in ~~Physician Global Activity~~ PhGA ~~VAS~~ over time Physician Global Activity (PhGA) ~~VAS~~ ~~Physician Global Activity VAS~~ PhGA ≥1.5 cm ~~Physician Global Activity~~ PhGA is a partially validated tool… ~~Physician Global Activity~~ PhGA ~~VAS~~ Worsening of the ~~Physician Global Activity~~ PhGA by ≥2 cm on a 10-cm VAS and worsening of findings of MMT-8 by ≥20% from baseline ~~Physician assessed global~~ PhGA worsening by ≥2 cm on a 10-cm VAS and worsening on ~~manual muscle testing~~ MMT-8 by ≥20%	Language describing the Physician Global Activity was revised to clarify it.
1.1 Synopsis Tertiary Endpoints 1.3.Schedule of Activities (SoA) Time and Events Schedule 3.OBJECTIVES AND ENDPOINTS ENDPOINTS Tertiary Endpoints 8.1.1.2. Patient Global Activity 8.1.2.1. IMACS TIS	Mean change from baseline in Patient Global Activity (PtGA) ~~VAS~~ at Week 24 The proportion of participants with improvement in ~~Patient Global Activity~~ PtGA ~~VAS~~ at Week 24 Mean change from baseline in ~~Patient Global Activity~~ PtGA ~~VAS~~ over time The proportion of participants with improvement in ~~Patient Global Activity~~ PtGA ~~VAS~~ over time Patient Global Activity (PtGA) ~~VAS~~ ~~Patient Global Activity~~ PtGA is a partially validated tool …. ~~Patient Global Activity~~ PtGA ~~VAS~~	Language describing the Patient Global Activity was revised to clarify it.
1.1 Synopsis EFFICACY	Measures of global disease activity: ~~Physician Global Activity~~ PhGA and ~~Patient Global Activity~~	Language describing the Physician and Patient Global Activity was

Section number and Name	Description of Change	Brief Rationale
EVALUATIONS	PtGA for global evaluation of the patient's overall disease activity at the time of assessment using a 10 cm Visual Analogue Scale (VAS).	revised to clarify it.
1.1 Synopsis Tertiary Endpoints 3.OBJECTIVES AND ENDPOINTS ENDPOINTS Tertiary Endpoints 8.1.1.6. Physical Function (Health Assessment Questionnaire Disability Index) 8.1.2.1. IMACS TIS	Mean change from baseline in ~~Functional Assessment~~ Physical Function (Health Assessment Questionnaire Disability Index [HAQ-DI]) at Week 24 The proportion of participants with improvement in ~~Functional Assessment~~ Physical Function (HAQ-DI) at Week 24 Mean change from baseline in ~~Functional Assessment~~ Physical Function (HAQ-DI) over time The proportion of participants with improvement in ~~Functional Assessment~~ Physical Function (HAQ-DI) over time ~~Functional Assessment~~ Physical Function (Health Assessment Questionnaire Disability Index) ~~Functional Assessment~~ Physical Function (HAQ-DI)	Language describing the HAQ-DI was revised to clarify it.
1.1 Synopsis Tertiary Endpoints 3.OBJECTIVES AND ENDPOINTS ENDPOINTS Tertiary Endpoints	Mean change from baseline in 36-item short form (SF-36) including individual domains and component summary (PCS, MCS) score**s** ~~survey~~ at Week 24 The proportion of participants with improvement in SF-36 including individual domains and component summary (PCS, MCS) score**s** ~~survey~~ at Week 24 Mean change from baseline in SF-36 including individual domains and component summary (PCS, MCS) score**s** over time The proportion of participants with improvement in SF-36 including individual domains and component summary (PCS, MCS) score**s** over time	Language describing the SF-36 was revised to clarify it.
1.1 Synopsis EFFICACY EVALUATIONS	Patient-reported outcomes (PROs): Health Assessment Questionnaire Disability Index (HAQ-DI) for physical function ~~functional assessment~~ and, SF-36 survey to assess generic health-related quality of life (HRQOL) ~~for global medical quality of life, functional health, well-being of the participants, and FI 2~~.	Language describing the HAQ-DI and SF-36 was revised to clarify it.
1.1 Synopsis Secondary Efficacy Analysis	Analyses comparing the 2 treatment arms will be performed using a logistic model similar to primary analysis with the binary outcome related to individual core set measures at Week 24. ~~Analyses comparing the 2 treatment arms with regard to ≥20% reduction from baseline for individual core set measures at Week 24 will be performed using a logistic model similar to primary~~	Text was revised to ensure a consistent description of the body.

Section number and Name	Description of Change	Brief Rationale
	~~analysis.~~	
1.3.Schedule of Activities (SoA) Time and Events Schedule Footnote b.	It is strongly recommended that participants who permanently discontinue study drug, but do not withdraw from study participation, be followed at all subsequent study visits through Week 80. ~~At a minimum, participants who permanently discontinue study drug, but do not withdraw from study participation, should return for a follow-up visit 8 weeks after the last study drug administration to undergo procedures as outlined for the EO-Treatment visit.~~ Participants, who permanently discontinue study drug administrations on or before the Week 72 visit, but do not withdraw from study participation, must undergo procedures for safety follow-up visits (postdiscontinuation) as outlined for the end of trial (EO-Treatment) visit as soon as possible on or before next scheduled visit. Participants, who permanently discontinue study drug administrations on or before the Week 72 visit, and withdraw from study participation, must undergo procedures for safety follow-up visits (postdiscontinuation) as outlined for the end of trial (EO-Treatment) visit as soon as possible on or before next scheduled visit, and must return approximately 8 weeks after last study drug administration to undergo procedures for safety follow-up visits (8 weeks postdiscontinuation) as outlined for the end of trial (EO-Treatment). If the interval between postdiscontinuation visit and 8 weeks postdiscontinuation visit is less than two weeks, can skip 8 weeks postdiscontinuation.	Text was revised to clarify the action in case that participants permanently discontinue study drug.
1.3.Schedule of Activities (SoA) Time and Events Schedule Footnote c.	Participants, who discontinue study drug administrations on or before the Week 72 visit, and withdraw from study participation, must return approximately 16 weeks after last study drug administration to undergo procedures for safety follow-up visits as outlined for the end of trial (EO-Trial) visit.	Text was revised to clarify the action in case that participants permanently discontinue study drug.
2.2. Background	The cumulative global exposure (through 31 December 2018~~7~~) has been estimated as 1,375,007~~1,036,701~~ person-years.	Text was revised to update the latest information.
4.3. Justification for Dose	Results from a Phase 2 study of ustekinumab in SLE has suggested the effectiveness of ustekinumab in patients with SLE. PK parameters of ustekinumab have, in general, been similar across multiple indications, including psoriasis, PsA, Crohn's disease, and SLE after correcting for body weight-related PK differences. Study CNTO1275SLE2001 has shown that treatment with ustekinumab administered as an ~6 mg/kg IV dose following by 90 mg SC dose at Week 8 and then every 8 weeks thereafter was efficacious and generally well tolerated in subjects with SLE. The safety profile of this dose regimen in the CNTO1275SLE2001 study was consistent with the	Text was added to clarify the Justification for Dose.

Section number and Name	Description of Change	Brief Rationale
	well-established profile observed in several large-scale Phase 3 Crohn's disease studies. Taking the overlapping features of PM/DM and SLE into account, the planned regimen may be effective in patients with PM/DM.	
5.1.Inclusion Criteria 6.	Must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel ~~including liver enzymes~~, other specific tests, blood coagulation, hematology, or urinalysis except for items specified in Inclusion Criteria #20 and 21 are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initiated by the investigator.	Text was revised to clarify the inclusion criteria for the clinical laboratory test.
5.1.Inclusion Criteria 8.	If a participant with PM did not have history of muscle biopsy, score of classification cannot be calculated. If a participant with DM did not have history of muscle biopsy, score of classification must be calculated based on score without muscle biopsy.	Text was revised to clarify the inclusion criteria for the history of biopsy at the classification.
5.1.Inclusion Criteria 12.	-MMF ≤3 g/day ~~and/or~~ -AZA 1 to ~~≤~~2 mg/kg/day; up to 3 mg/kg/day ~~100 mg/day~~	Text was revised to clarify the inclusion criteria for the standard of treatment based on the package insert.
5.1.Inclusion Criteria 13.	Regular or as needed treatment with topical use of medium/mild (Group IV) or weak ~~low~~ (Group V ~~Class VI, VII~~) potency glucocorticoids ~~(according to the World Health Organization classification of topical glucocorticoids)~~ are permitted to treat skin lesions of DM on a stable dose for ≥2 weeks prior to first dose of the study drug.	The criteria for topical use of glucocorticoids was revised based on the medical practice in Japan.
5.1.Inclusion Criteria 19.	a. Have no history of latent or active TB prior to screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB at least 3 weeks prior to the first administration of the study drug, or have documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of the study drug.	The criteria for treatment of latent TB was revised based on the medical practice in Japan.
5.2.Exclusion Criteria 1.	Has myositis other than PM/DM, including but not limited to ADM, clinically amyopathic DM, juvenile DM, inclusion body myositis (IBM), immune-mediated necrotizing myopathy diagnosed based on muscle biopsy findings and positive anti-SRP or anti-HMGCR antibody, drug-induced myositis, PM associated with human immunodeficiency virus (HIV), ~~and~~ muscular dystrophy, congenital myopathy, metabolic myopathy, and mitochondrial myopathy.	Text was added to clarify the exclusion criteria for the myopathy.
5.2.Exclusion	Has ~~clinical evidence of~~ severe or progressive ILD,	Text was revised and added to

Section number and Name	Description of Change	Brief Rationale
Criteria 3.	which was confirmed by the investigator based on HRCT findings, clinical course consistent with ILD, and consultation with a pulmonologist. Findings from HRCT at screening should not show clinically significant worsening compared to past HRCT or comparable CT results taken at least 3 months before screening. ~~Other clinical evidence includes~~ The eligibility of ILD may be determined considering the following but not limited to; • Presence of dyspnea on exertion with normal activities of daily living or low grade exertion (eg, walking), or a recent change in exercise tolerance due to dyspnea	clarify the exclusion criteria for severe or progressive ILD.
5.2.Exclusion Criteria 15.	Has received prior IV immunoglobulin (Ig) or immunomodulatory biologic therapy not described in Section 6.6, Prohibited Therapies such as guselkumab, risankizumab, belimumab, epratuzumab, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, or agents whose mechanism of action targets B cell, tumor necrosis factor alpha (TNFα), IL-1, IL-2, IL-6, IL-17, IL-23, or IFN pathways, within ~~less than~~ 5 half-lives or 12 weeks ~~3 months~~, whichever is longer, prior to first dose of the study drug. Has received rituximab within 24 weeks ~~6 months~~ prior to first dose of the study drug.	Corrections were made to indicate the appropriate time period of exclusion criteria for concomitant treatments.
5.2.Exclusion Criteria 18.	Has received an investigational drug that is not previously defined in other exclusion criteria (including investigational vaccines, branched-chain amino acids, or other medications specified in Section 6.6) within 5 half-lives or 12 weeks ~~3 months~~, whichever is longer, or used an invasive investigational medical device within 12 weeks ~~3 months~~ before the planned first dose of the study drug, or is currently enrolled in an interventional study.	Corrections were made to indicate the appropriate time period of exclusion criteria for concomitant treatments.
5.2.Exclusion Criteria 22.	Use of apheresis therapy (including but not limited to plasmapheresis, photopheresis, leukocytapheresis), or immunoadsorption is prohibited within 24 weeks ~~6 months~~ prior to the first administration of the study drug.	Corrections were made to indicate the appropriate time period of exclusion criteria for concomitant treatments.
5.3. Lifestyle Considerations 3.	Agree to use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline until the last dose of the study drug for participants with DM.	Text was revised to clarify the Lifestyle Considerations for participants with DM.
6.1.Study Drugs Administered	At Week 24, participants receiving placebo will crossover to receive body weight-range based IV administration of ustekinumab. At Week 24, it is recommended that SC dosing is administrated after completion of IV administration. SC dosing may be administered before assessment of infusion reactions. However, IV and SC administration to	Text was added to clarify the procedure of study drug administration at Week 24.

Section number and Name	Description of Change	Brief Rationale
	the same limb should be avoided**.** Starting at Week 32, all participants will receive ustekinumab 90 mg SC q8w through Week 72.	
6.5.1.Prestudy and Concomitant Medications Through Week 80	Limitation of concomitant medications must be followed through Week 80. ~~The change of administration route is allowed if the equivalent dose of the substitution remains the same and the substitution is considered as a systemic treatment.~~	Text was revised to clarify the change of administration for the concomitant medications through Week 80.
6.5.4. Topical Medications	For the treatment of cutaneous lesion in participants with DM, regular use of topical medications ~~glucocorticoid~~ is permitted. However, topical compounds cannot include a prohibited medication**.** ~~These~~ Topical glucocorticoids must be medium/mild (Group IV) or weak (Group V) ~~low (Class VI, VII)~~ potency glucocorticoids. ~~(according to the World Health Organization classification of topical glucocorticoids)~~ "As needed" use of topical medium/mild (Group IV) or weak (Group V) potency glucocorticoids is permitted, but not within ~~with no changes in dose for ≥2 weeks prior to first dose of study drug and during the study. These topical glucocorticoids should not be used for~~ 48 hours prior to a study visit. After discussion with the sponsor, topical glucocorticoids of strong (Group III) or weaker potency may be used on skin lesion up to 2 weeks where there is no preexisting skin eruptions of DM in case it is considered due to adverse events other than DM.	The criteria for topical use of glucocorticoids was revised based on the medical practice in Japan.
6.6. Prohibited Therapies	Epidural, IV, SC, IM, intra-articular, intrabursal, or intralesional administration of~~Intravenous~~ glucocorticoids	Text was revised to clarify the details of glucocorticoids in prohibited therapies.
7.1. Discontinuation of Study Drug	The participant requires high dose glucocorticoid (≥1 mg/kg/day of prednisolone or equivalent) for >2 weeks or a prohibited therapy such as a biologic, cyclophosphamide, or IV glucocorticoid (see Section 6.6) ~~then the participant must be discontinue from the study~~. If a new immunomodulator or oral glucocorticoid (<1 mg/kg/day of prednisolone or equivalent) that is permitted per-protocol is initiated, then a participant will be considered a treatment failure but will not need to discontinue the study drug administrations ~~be withdrawn from the study~~. Addition of new therapy for PM/DM activity must be discussed with the sponsor to determine the suitability of the participant to continue the study drug administrations ~~participating in the study~~.	Corrections were made to indicate the appropriate procedure in case that new immunomodulator, oral or high dose glucocorticoid are required.
8. STUDY ASSESSMENTS AND PROCEDURES 8.6.1. Evaluations	The total blood volume to be collected from each participant will be approximately 750 ~~700~~ mL.	Corrections were made because of the change of laboratory kit.
8.2.5. Interstitial Lung Diseases and	All participants must be monitored with SpO_2, chest x-ray, laboratory data (KL-6 and SP-D), chest	Text was added to clarify the additional safety data which IDMC

Section number and Name	Description of Change	Brief Rationale
Respiratory Muscle	HRCT, and PFT as scheduled in Section 1.3 during the study. The investigator may consider additional examination including C-reactive protein, ferritin, and blood gas analysis as needed. In case of worsening or new onset of lung lesion, it is recommended to make a differential diagnosis of fungal infection, cytomegalovirus infection, heart failure and/or other cause using additional laboratory data such as β-D-glucan, C7-HRP, and/or BNP. If the investigator identifies new onset or worsening of ILD or observes any finding which needs to be evaluated by a pulmonologist, the investigator should consider consultation with a pulmonologist and administer rescue treatment as needed. Permanent discontinuation of the study drug must be considered for participants who experience worsening of ILD or newly identified severe ILD that is considered serious or severe by the investigator in cases of the following but not limited to; • Significant worsening of ILD findings based on chest x-ray or HRCT • Significant decrease in SpO_2 such as $SpO_2 <$ 90% or a decrease of SpO_2 by 5% or more	members recommended.
8.3.2. Method of Detecting Adverse Events and Serious Adverse Events	**Solicited Adverse Events** Solicited AEs are ~~predefined local and systemic~~ events ~~for which the participant is specifically questioned and~~ which are noted by participants in their participant diary (see Section 8, Study Assessments and Procedures). **Unsolicited Adverse Events** Unsolicited AEs are all AEs other than solicited AEs as defined above ~~for which the participant is not specifically questioned in the participant diary~~.	Corrections were made to indicate the appropriate these AE definitions based on the actual participants diary.
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events	~~The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements in which the studies are conducted.~~	The text was revised to keep a consistency with Japanese regulatory requirements.
8.5. Treatment of Overdose	For this study, any dose of ustekinumab greater than set daily dose at Section 6.1 within 2 weeks ~~a 24 hour~~ time period will be considered an overdose.	The text was revised to keep a consistency with other ustekinumab study protocols.
8.7. Genetics	A pharmacogenomic blood sample (whole blood DNA) will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional. DNA samples will be analyzed for identification of genetic factors to better understand the molecular effects of ustekinumab and/or susceptibility to PM/DM, and to evaluate markers that can predict clinical response. Such analysis may include the human leukocyte antigen (HLA) alleles and any	Text was added to clarify the genetics analysis.

Section number and Name	Description of Change	Brief Rationale
	relevant single nucleotide polymorphisms that are reported to be associated with ustekinumab and/or the development of PM/DM.	
9.5.1. Independent Data Monitoring Committee	After the review, the IDMC will make recommendations to the Sponsor Committee who is separate from the study team regarding the continuation of the study. The details will be provided in a separate IDMC charter. As needed basis, the IDMC might ask the study team to provide with further information via the IDMC bureau. The study team make the best effort to collect the further information from each investigational site for the evaluation by the IDMC. The IDMC will consist of 2 medical experts in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter. The study team is defined as a cross-functional team responsible for the planning, initiation, execution, analysis, and reporting of a trial. This may include but is not limited to: Study Responsible Physician/Scientist, Global Data Manager, Global Trial Manager, Central Monitoring Manager, Site Manager, Local Trial Manager, Study Programmer, Study Statistician, Quality Monitoring & Compliance representative, Clinical Pharmacology representative, and Patient Reported Outcomes Group Leader.	Text was added to clarify the additional data which IDMC members recommended, procedure to obtain them and a definition of the study team.
10.8. Appendix 8: Cancer Screening Test	**Cancer** / **Assessments for screening** / **Age** / **Sex** Lung cancer / Medical interview, Chest x ray and Sputum cytology* / ≥40 / Male and Female * This cytology is needed for participants are ≥50 years old and meet smoking index (number of cigarettes smoked per day x years) is ≥ 600.	Text was added to clarify the needed participants for the sputum cytology based on medical practice in Japan and study investigator's comment.
10.9. Appendix 9: Hepatitis B Virus Screening	Added the all contents	The appendix was added to clarify the criteria for Hepatitis B Virus Screening.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

11. REFERENCES

1. Aggarwal R, Rider LG, Ruperto N, et al; International Myositis Assessment and Clinical Studies Group and the Paediatric Rheumatology International Trials Organisation. 2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Adult Dermatomyositis and Polymyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol. 2017 May;69(5):898-910.
2. Alexanderson H, Broman L, Tollbäck A, Josefson A, Lundberg IE, Stenström CH. Functional index-2: Validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum.2006 Feb 15;55(1):114-122.
3. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. Chichester, England: Wiley, 2009.
4. Bronner IM, van der Meulen MF, de Visser M, et al. Long-term outcome in polymyositis and dermatomyositis. Ann Rheum Dis. 2006 Nov;65(11):1456-1461.
5. David T, Ling SF, Barton A. Genetics of immune-mediated inflammatory diseases. Clin Exp Immunol. 2018 Jul;193(1):3-12.
6. Espinosa-Ortega F, Gómez-Martin D, Santana-De Anda K, Romo-Tena J, Villaseñor-Ovies P, Alcocer-Varela J. Quantitative T cell subsets profile in peripheral blood from patients with idiopathic inflammatory myopathies: tilting the balance towards proinflammatory and pro-apoptotic subsets. Clin Exp Immunol. 2015 Mar;179(3):520-528.
7. Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med. 1993 Jul;86(7):447-458.
8. Igarashi A, Kato T, Kato M, Song M, Nakagawa H; Japanese Ustekinumab Study Group. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012. 39(3):242-252.
9. Investigator's Brochure: CNTO1275 (Ustekinumab), Edition 19. Janssen Research & Development (31 May 2018).
10. Kageyama T, Suto A, Iwamoto T, et al. IL-21 exacerbates autoimmune myositis by enhancing the accumulation of GM-CSF-producing γδ T cells in the muscle. Immuno Horizons 2017;1(8):176-187.
11. Kondo M, Murakawa Y, Harashima N, Kobayashi S, Yamaguchi S, Harada M. Roles of proinflammatory cytokines and the Fas/Fas ligand interaction in the pathogenesis of inflammatory myopathies. Immunology. 2009 Sep;128(1 Suppl):e589-e599.
12. Liu T, Hou Y, Dai TJ, Yan CZ. Upregulation of Interleukin 21 and Interleukin 21 Receptor in Patients with Dermatomyositis and Polymyositis. Chin Med J (Engl). 2017 Sep 5;130(17):2101-2106.
13. Miller FW, Cooper RG, Vencovský J, et al. Myositis Genetics Consortium. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. Arthritis Rheum. 2013 Dec;65(12):3239-3247.
14. Montoya CL, Gonzalez ML, Ospina FE, Tobón GJ. A Rare Case of Amyopathic Juvenile Dermatomyositis Associated With Psoriasis Successfully Treated With Ustekinumab. J Clin Rheumatol. 2017 Mar;23(2):129-130.
15. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol. 2011. 70(3):427-436.
16. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum. 2013. 65(2):314-324.
17. Page G, Chevrel G, Miossec P. Anatomic localization of immature and mature dendritic cell subsets in dermatomyositis and polymyositis: Interaction with chemokines and Th1 cytokine-producing cells. Arthritis Rheum. 2004 Jan;50(1):199-208.

18. Proschan MA, Lan KKG, Wittes JT. Statistical Monitoring of Clinical Trials: A Unified Approach, Springer, 2006.

19. Rider LG, Werth VP, Huber AM, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S118-157.

20. Sasaki H, Kohsaka H. Current diagnosis and treatment of polymyositis and dermatomyositis. Mod Rheumatol. 2018 Nov;28(6):913-921.

21. Schmitt N, Morita R, Bourdery L, et al. Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12. Immunity. 2009 Jul 17;31(1):158-169.

22. Shen H, Xia L, Lu J, Xiao W. Interleukin-17 and interleukin-23 in patients with polymyositis and dermatomyositis. Scand J Rheumatol. 2011 May;40(3):217-220.

23. Thompson C, Piguet V, Choy E. The pathogenesis of dermatomyositis. Br J Dermatol. 2018 Dec;179(6):1256-1262.

24. Tjarnlund A, Tang Q, Wich C, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomized, phase IIb treatment delayed-start trial. Ann Rheum Dis. 2018. 77(1):55-62.

25. Tournadre A, Lenief V, Eljaafari A, Miossec P. Immature muscle precursors are a source of interferon-β in myositis: role of Toll-like receptor 3 activation and contribution to HLA class I up-regulation. Arthritis Rheum. 2012 Feb;64(2):533-541.

26. Tournadre A, Miossec P. A critical role for immature muscle precursors in myositis. Nat Rev Rheumatol. 2013 Jul;9(7):438-442.

27. Umezawa N, Kawahata K, Kimura N, Yoshihashi-Nakazato Y, Kohsaka H. Inhibition of IL-23 ameliorated murine model of polymyositis. Modern Rheumatology Abstract Supplement, The 61st annual scientific Meeting of the Japan College of Rheumatology. 2017 S192.

28. van de Vlekkert J, Hoogendijk JE, de Haan RJ, et al; Dexa Myositis Trial. Oral dexamethasone pulse therapy versus daily prednisolone in sub-acute onset myositis, a randomized clinical trial. Neuromuscul Disord. 2010 Jun;20(6):382-389.

29. Whiting-O'Keefe QE, Stone JH, Hellmann DB. Validity of a vasculitis activity index for systemic necrotizing vasculitis. Arthritis Rheum. 1999 Nov;42(11):2365-2371.

30. Wong D, Kea B, Pesich R, et al. Interferon and biologic signatures in dermatomyositis skin: specificity and heterogeneity across diseases. PLoS One. 2012;7(1):e29161.

31. Zhou Y, Li X, Wang G, Li X. Association of FAM167A-BLK rs2736340 Polymorphism with Susceptibility to Autoimmune Diseases: A Meta-Analysis. Immunol Invest. 2016 May;45(4):336-348.

32. Zong M, Dorph C, Dastmalchi M, et al. Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. Ann Rheum Dis. 2014. 73(5):913-920.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.*

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	29-Nov-2021 06:30:04 (GMT)	Document Approval

Janssen Pharmaceutical K.K.*

Clinical Protocol

COVID-19 Appendix

Protocol Title

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. The sponsor is identified on the Protocol Supplementary Information, which will be provided as a separate document.

Status: Approved
Date: 9 Jun 2020
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-78936, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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 participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study -related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for study intervention and follow-up.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the Sponsor and Investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures eg, those related to safety monitoring / efficacy evaluation / study drug storage and administration (including training where pertinent)
    - procurement of study drug by patients (or designee) or shipment of study drug from the study site directly to patients for at home administration (including the potential for patient self-administration of study drug)
    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
    - other procedures, eg, imaging, may be conducted at an appropriate facility
- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).
    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed Sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The Sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).
- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:
    - During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection

(clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

(i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

AND

(ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

- NOTES on COVID-related exclusion:

1. If a patient is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Janssen Pharmaceutical K.K.*

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	09-Jun-2020 03:27:35 (GMT)	Document Approval