Protocol C0251008

AN OPEN LABEL, LONG-TERM EXTENSION STUDY TO INVESTIGATE THE SAFETY OF PF-06823859 ADMINISTERED TO ADULT PARTICIPANTS ≥18 AND ≤80 WITH ACTIVE DERMATOMYOSITIS

Statistical Analysis Plan
(SAP)

Version: 1

Date: 30 Nov 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 30 Nov 2021	Original 3 Sept 2021	N/A	N/A

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C0251008. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Table 2. List of Study Objectives, Estimands, and Endpoints

Objectives	*Endpoints*	*Estimands*
Primary:	***Primary:***	***Primary:***
• *To evaluate the long-term safety and tolerability of PF-06823859.*	• *Incidence of AEs, laboratory abnormalities, changes in vital signs, and ECG findings.*	• *There are no defined estimands for safety and tolerability endpoints; these will be analyzed using Pfizer data standards, as applicable.*
Secondary:	***Secondary:***	***Secondary:***
• *To evaluate the long-term efficacy of PF-06823859 in adult participants with moderate to severe DM.*	• *Change from baseline in CDASI activity score at Week 52.*	• *E1: This estimand uses a hypothetical estimand strategy (ICH E9 addendum) estimating the mean effect of PF-06823859 in the absence of intercurrent events (study withdrawal). This is the mean change from baseline to Week 52 CDASI activity score for all randomized and dosed participants with non-missing baseline score in the (a) Skin Analysis Set and (b) Muscle*

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	• *Absolute values and change from baseline of CDASI activity and CDASI damage scores at all scheduled timepoints.* • *TIS score at Week 52 and at intermediate scheduled timepoints for participants who entered from Stage 3 of Protocol C0251002.* • *Change from baseline in the CSMs of the TIS including PhGA, PtGA, MMT-8, HAQ-DI, muscle enzymes, and MDAAT at Week 52 and at intermediate scheduled timepoints.*	*Analysis Set (see details in Section 4).* • *These additional CDASI endpoints will be analyzed using E1 at all scheduled timepoints.* • *E2: This estimand uses a hypothetical estimand strategy (ICH E9 addendum) estimating the mean effect of PF-06823859 in the absence of intercurrent events (study withdrawal). This is the mean TIS at Week 52 for all randomized and dosed participants included with non-missing baseline score in the Muscle Analysis Set (see details in Section 4).* • *The endpoints for the CSM of the TIS will be analyzed using E2 at Week 52 and all intermediate scheduled timepoints.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***	***Tertiary/Exploratory:***
• *To characterize pharmacokinetics (PK) of PF-06823859.* • *To characterize pharmacodynamics (PD) effects of PF-06823859.* • *To evaluate immunogenicity of PF-06823859.* • *To evaluate the effect of PF-06823859 on suicidality assessment over time in participants with active DM.* • *To evaluate the effect of PF-06823859 on SF-36*	• *Plasma concentrations of PF-06823859.* • *Absolute values and change from baseline in the values of selected biomarkers at all scheduled time points.* • *Incidence of ADA and NAb.* • *Absolute values and change from baseline values of Columbia-Suicide Severity*	• *Not applicable.*

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(v2 acute) and EQ-5D-5L PROs.	*Rating Scale (C-SSRS) at all scheduled time points.* • *Absolute values and change from baseline in the values of PROs including SF-36 (v2 acute) and EQ-5D-5L at all scheduled timepoints.*	

2.1.1. Primary Estimand(s)

There are no defined estimands for the incidence of AEs, laboratory abnormalities, changes in vital signs, and ECG findings. These endpoints will be analyzed using Pfizer data standards as applicable. All participants who receive at least 1 dose of IP will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

2.1.2. Secondary Estimand(s)

Two estimands are defined for this study. ***Estimand 1*** *(E1) will support specified CDASI assessments at specified timepoints for participants in the Skin Analysis Set and Muscle Analysis Set separately.* ***Estimand 2*** *(E2) will support TIS and CSM assessments at specified timepoints for participants in the Muscle Analysis Set.*

E1 will be the population average effect of PF-06823859 on CFB in CDASI activity score at Week 52 for all randomized and dosed participants with non-missing baseline in a specified analysis set (Skin or Muscle Analysis Set) in the absence of dropout. Measurements taken after a participant withdraws from treatment will be censored and treated as missing data. The population-based estimate for the effect of PF-06823859 will be the mean CFB in CDASI-activity score at Week 52.

E1 will also be applied to each combination of the following endpoints, timepoints, and analysis sets:

- *Endpoints: Change from baseline and absolute values of CDASI activity score and CDASI damage score;*
- *Timepoints: Week 52 and all scheduled intermediate timepoints;*
- *Analysis sets: Skin Analysis Set and Muscle Analysis Set.*

E2 will be the population average estimate for the effect of PF-06823859 on TIS at Week 52 for all randomized and dosed participants with non-missing baseline in the Stage 3 Muscle Analysis Set in the absence of dropouts. Measurements taken after a participant withdraws from treatment will be censored and treated as missing data. The population-based estimate for the effect of PF-06823859 will be the mean TIS at Week 52.

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E2 will also be applied to each combination of the following endpoints and timepoints in the Stage 3 Analysis Set:

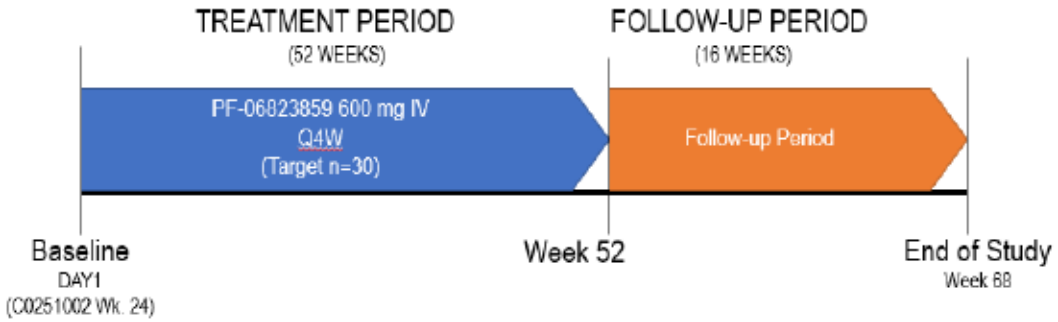
- *Endpoints: TIS and change from baseline in each of the CSM of the TIS.*
- *Timepoints: Week 52 and all scheduled intermediate timepoints.*

2.2. Study Design

This is a Phase 2b, OLE study to evaluate the long-term safety and tolerability of PF-06823859 in adult participants with moderate to severe DM who completed the treatment period of a qualifying study (including Protocol C0251002) and have agreement from their study doctor to continue active treatment. Eligible participants will not have had any significant protocol deviations (eg, not following the protocol, taking prohibited medications, not using appropriate contraception) or have not completed all study treatment in the qualifying study. Approximately 30 participants who complete the Week 24 visit during the treatment period in Study C0251002 or equivalent in another qualifying study, may be enrolled in Protocol C0251008. The treatment duration of OLE study participation will be up to 48 weeks (treatment period is up through and including Week 52), with a 16 week follow up period. See Figure 1 for the study schematic.

Qualified participants will be randomized to receive open-label PF-06823859 600 mg IV every 4 weeks for up to 48 weeks, however the treatment period is up to Week 52. All participants will be followed for another 16 weeks in the Follow-up Period. Participants who are discontinued from study intervention will also enter the follow-up period.

Figure 1. Study Schema



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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

For the skin cohort (ie, participants entering C0251008 from Amended Stage 2 of C0251002), the major efficacy analyses assess changes in the modified CDASI *activity* and *damage* scores. The details of the calculation of these scores are presented in Section 9.2.

For the muscle cohort (ie, participants entering C0251008 from Stage 3 of C0251002), the major efficacy analyses assess changes in the modified CDASI activity and damage scores *and* changes in the TIS and the CSM. The details of the calculation of the TIS are presented in Section 9.3.

Safety assessments for the primary endpoint will be reported for all participants and by cohort. Efficacy assessments will generally be reported by cohort.

Unless specifically stated otherwise, the baseline value for all assessments is defined as the last non-missing measurement collected prior to the first administration of study drug at Day 1. Change from baseline is defined as the value at a specific visit minus the value from baseline.

3.1. Primary Endpoint(s)

3.1.1. Incidence of Adverse Events (AEs)

Reporting for AEs is described in Section 6.6.1. Appendix 3 of the C0251008 Study Protocol provides definitions for an AE and SAE. An AE is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

3.1.2. Laboratory Abnormalities

Reporting for laboratory data is described in Section 6.6.2. To determine if there are any clinically significant laboratory abnormalities, the safety laboratory tests will be assessed against the criteria specified in the C0251008 Study Protocol. Baseline of safety laboratory tests will be the last pre-dose measurement.

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3.1.3. Changes in Vital Signs

Vital signs (including blood pressure, pulse, respiratory rates and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities. Baseline will be the last measurement prior to receiving study treatment. Reporting for changes in vital signs is described in Section 6.6.3.

3.1.4. ECG Findings

Reporting for ECG findings is described in Section 6.6.4. Baseline will be the last measurement prior to receiving study treatment.

3.2. Secondary Endpoint(s)

3.2.1. CDASI Activity and Damage Scores

The CDASI activity and damage scores are continuous measures with ranges of 0-100 and 0-32 respectively, where higher scores indicate higher levels of disability. Both CDASI scores are computed as the sum of component scores as described in Appendix 9.2. The absolute value and change from baseline (CFB) values of the CDASI activity and damage scores will be assessed.

3.2.2. TIS

The TIS is a continuous measure ranging from 0 to 100 that assesses disease activity relative to baseline. By definition, all participants have a TIS of 0 at baseline. A TIS $\geq$20 represents minimal improvement, TIS $\geq$40 represents moderate improvement, and TIS $\geq$60 represents major improvement.

Six CSMs contribute to the TIS, including the PhGA, PtGA, MMT-8, HAQ-DI, global extramuscular disease activity assessment from the MDAAT, and muscle enzymes. The TIS is the sum of all 6 improvement scores associated with the change in each CSM. Appendix 9.3 provides full details on the computation of the TIS and each CSM. The absolute values and CFB in each CSM will be assessed.

3.2.2.1. PhGA

Physician Global Assessment Score (PhGA) is defined as a value within (0-100 mm or 0-10 cm) on a visual analog scale. For computation of the TIS, the PhGA is drawn from the MDAAT. Higher scores indicate a higher level of disability.

3.2.2.2. PtGA

Patient Global Assessment Score (PtGA) is defined as a value within (0-100 mm or 0-10 cm) on a visual analog scale. Higher scores indicate a higher level of disability.

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3.2.2.3. MMT-8

MMT-8 is a tool that assesses muscle strength using manual muscle testing. Eight designated muscles are tested unilaterially with a total potential summed score of 0-80. Lower scores indicate a higher level of disability.

3.2.2.4. HAQ-DI

The HAQ-DI contains eight sections (including dressing & grooming, arising, eating, walking, hygiene, grip, reach, and activities) with items that can be scored from 0 to 3. Higher scores indicate higher level of disability. The HAQ-DI score used in the CSM calculation for the TIS is the average of these scores.

3.2.2.5. Global Extramuscular Disease Activity Assessment from the MDAAT

The global extramuscular disease activity assessment from the MDAAT is one of the CSMs used in the computation of the TIS. The global extramuscular disease activity is defined as a value within 0-10 cm on a visual analog scale. Higher scores indicate higher level of disability.

3.2.2.6. Muscle Enzymes

Five muscle enzymes are assessed for the TIS, including aldolase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and creatine kinase. The most abnormal serum muscle enzyme among these is used in the computation of the muscle enzyme CSM of the TIS.

3.3. Other Endpoint(s)

3.3.1. PK and PD Endpoints

The PK/PD endpoints include:

- Plasma PF-06823859 concentrations.
- PD biomarkers: total IFNβ, hsCRP, muscle biomarkers described in Section 3.2.2.6.

The absolute value and CFB will be assessed for each biomarker.

3.3.2. Immunogenicity

Immunogenicity will be assessed through reporting the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs).

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3.3.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is used to assess suicidal ideation and behavior during the conduct of the study. The C-SSRS is a patient-reported questionnaire administered by the investigator or site staff that have been trained to administer the test. The absolute value and CFB in the C-SSRS will be assessed.

3.3.4. PROs

- European Quality of Life – 5 Dimensions-5 Level (EQ-5D-5L) Questionnaire assesses impact on health-related quality of life in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the 5 domains may be used to calculate a single index value, also known as a utility score. Higher scores indicate higher level of disability. The absolute value and CFB in the EQ-5D-5L will be assessed.

- The SF-36 v.2 (Acute version) is a 36-item generic health status measure. It measures 8 general health concepts or domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). These domains are also summarized as physical and mental component scores (PCS and MCS). Higher scores indicate lower level of disability. The absolute value and CFB in the SF-36 v.2 scores will be assessed.

3.4. Baseline Variables

Unless specifically stated otherwise, the baseline value for all assessments is defined as the last non-missing measurement collected prior to the first administration of study drug at Day 1. *References to "baseline" in this study correspond to the Week 24 visit of the Phase 2 C0251002 study and Day 1 of this study.*

3.5. Safety Endpoints

Safety endpoints are described in Section 3.1.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

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Participant Analysis Set	Description
Randomized	*"Randomized" means a participant's agreement to participate in a clinical study following completion of the informed consent process. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity.*
Full Analysis Set (FAS)	*All participants enrolled who take at least 1 dose of study intervention.*
Safety Analysis Set	*All participants enrolled who take at least 1 dose of study intervention. This includes all such participants regardless of which parent study or stage the participant entered from.*
Skin Safety Analysis Set	*All participants with skin predominant DM who take at least 1 dose of study intervention including participants entering from Amended Stage 2 of the C0251002 protocol.*
Muscle Safety Analysis Set	*Al participants with muscle predominant DM who take at least 1 dose of study intervention including participants entering from Stage 3 of the C0251002 protocol.*
PK Concentration Set	All participants assigned to investigational study treatment and who take at least 1 dose of investigational product and have at least 1 measurable concentration.
PD Data Set	All participants assigned to investigational study treatment and who take at least 1 dose of investigational product and have at least 1 of the PD parameters of interest.
Immunogenicity assessment population	All enrolled subjects who received at least one dose of PF-06823859 with at least one post-treatment anti-PF-06823859 antibody determination.

Defined Analysis Set (Efficacy)	Description
Skin Analysis Set	*All participants with skin predominant DM in the FAS including participants who were enrolled in Amended Stage 2 of the C0251002 study.*
Muscle Analysis Set	*All participants with muscle predominant DM in the FAS including participants who were enrolled in Stage 3 of the C0251002 study.*

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Pooled Skin Analysis Set	*All participants in the FAS with a CDASI activity score of 14 or greater at baseline of study C0251002. This analysis set includes all subjects from Amended Stage 2 of the C0251002 study and potentially some subjects from Stage 3 of the C0251002 study who also have skin disease.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analyses will occur after database lock after Last Participant Last Visit (LPLV).

5.1. Hypotheses and Decision Rules

No statistical hypothesis testing is planned for this study.

5.2. General Methods

Analyses will generally be reported by cohort (skin or muscle). Sensitivity analyses will be performed for the CDASI activity score, CDASI damage score, and TIS. Supportive analyses for the CDASI activity and damage scores will use the pooled skin analysis set, which includes all participants from Amended Stage 2 of study C0251002 and participants from Stage 3 of study C0251002 with sufficient skin disease (see Section 4).

5.2.1. Analyses for Continuous Endpoints

For E1 and E2, the Longitudinal ANCOVA Model (LANCOVA, used for secondary analyses) and conventional analysis of covariance (ANCOVA, used for sensitivity analyses) methods will be used.

The LANCOVA analysis will use either the change from baseline value (CDASI activity or CDASI damage) or the direct value (TIS) as the continuous variable in the outcome in the model, which will be fit from baseline to Week 52. For the CFB CDASI activity and damage endpoints, the LANCOVA models will include week as a fixed effect and baseline value as a covariate. For the TIS, the LANCOVA model will include week as a fixed effect. In all models, an unstructured variance-covariance matrix will be used. Estimates and 90% CI will be reported. No p-values will be computed for the analysis.

5.3. Methods to Manage Missing Data

- In the longitudinal modeling (LANCOVA) of repeated measures of continuous outcomes (both efficacy measures and covariates) it is assumed that missing data are generated by the "missing at random" mechanism and, therefore imputation of the missing data is not necessary.

- In all data presentations of PK outcome (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of

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quantification). In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if concentration measurement was nor done or sample was not collected.

- The PK summary statistics will not be presented at a particular time point if more than 50% of the PK data are missing.
- Immunogenicity assay titers will be used to determine incidence for ADA and NAb. If a titer value is missing data imputation will not occur and missing values will be represented by NC (ie, not-calculated).
- For other endpoints, statistical analyses will be based on available data. Missing data will not be imputed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Incidence of AEs, Laboratory Abnormalities, Changes in Vital Signs, and ECG Findings

- Estimand strategy: Not applicable for safety endpoints.
- Analysis sets: Safety Analysis Set, Skin Safety Analysis Set, Muscle Safety Analysis Set.
- Analysis methodology: Descriptive statistics.
- Intercurrent events and missing data: Data after study withdrawal will be excluded; intermediate missing values will not be imputed.
- Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome (eg, BP, heart rate) will be summarized using N, mean, median, standard deviation, minimum, maximum. Change from baseline in laboratory data and vital signs will also be summarized according to sponsor Data Standards.

6.1.1.1. Sensitivity/Supplementary Analyses

6.2. Secondary Endpoint(s)

6.2.1. CDASI Activity and Damage Scores

6.2.1.1. Main Analysis

- Estimand strategy: E1.

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- Analysis sets: Skin Analysis Set and Muscle Analysis Set.
- Analysis methodology: Each CDASI endpoint (including CFB CDASI activity score, CFB CDASI damage score, absolute value of CDASI activity score, and absolute value of CDASI damage score) will be analyzed using LANCOVA including data from baseline to Week 52 with week as a fixed effect and baseline score as a covariate and an unstructed covariance matrix (Section 5.2.1).
- Intercurrent events and missing data: Data after study drug discontinuation will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed CDASI scores and change from baseline CDASI scores will be presented for each cohort for each CDASI endpoint.
- For each CDASI endpoint, the least-squares (LS) means and the 90% confidence interval for the LS means will be presented and plotted for all postbaseline visits.

6.2.1.2. Sensitivity and Supportive Analyses

- *Supportive*: For each CDASI endpoint, the analysis of Section 6.2.1.1 will be repeated using the Pooled Skin Analysis Set.

6.2.2. TIS

6.2.2.1. Main Analysis

- Estimand strategy: E2.
- Analysis sets: Muscle Analysis Set.
- Analysis methodology: The TIS will be analyzed using LANCOVA including data from baseline to Week 52 with week as a fixed effect and an unstructed covariance matrix (Section 5.2.1).
- Intercurrent events and missing data: Data after study drug discontinuation will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for the TIS will be presented.
- The LS means and the 90% confidence interval for the LS means will be presented and plotted for all postbaseline visits.

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6.2.2.2. Sensitivity and Supportive Analyses

- *Supportive*: the frequency and proportions of patients achieving minimal improvement (TIS≥20), moderate improvement (TIS ≥40) and major improvement (TIS ≥60) will also be reported for each postbaseline visit. 90% CIs will also be provided using Chan and Zhang's exact CI method.

6.2.3. CSMs

6.2.3.1. Main Analysis

- Estimand strategy: E2.
- Analysis sets: Muscle Analysis Set.
- Analysis methodology: The CFB in each CSM (including PhGA, PtGA, MMT-8, HAQ-DI, global extramuscular disease activity assessment from the MDAAT, and most abnormal muscle enzyme) will be analyzed using LANCOVA including data from baseline to Week 52 with week as a fixed effect and baseline score as a covariate and an unstructed covariance matrix (Section 5.2.1).
- Intercurrent events and missing data: Data after study drug discontinuation will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for the TIS will be presented.
- The LS means and the 90% confidence interval for the LS means will be presented and plotted for all postbaseline visits.

6.2.3.2. Sensitivity and Supportive Analyses

- *Supportive*: For each CSM at Week 52, the frequency and proportion of participants in each improvement category (as defined in Section 9.3) will be reported.
- *Supportive*: Summary statistics for the absolute value of each CSM, including the sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits will also be presented.

6.3. Other Endpoint(s)

6.3.1. PK Endpoints

- Analysis populations: PK concentration population.
- Analysis time points: all times with PK samples taken.

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- Analysis methodology: summary statistics will be provided for serum concentrations.
- Reporting results: Presentations for PF-06823859 concentrations will include:
  - a listing of all concentrations sorted by participant ID, cohort, and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
  - a summary of concentrations by nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (CV), minimum, maximum, and the number (percentage) of concentrations above the lower limit of quantification (LLQ).
  - median concentrations time plots (semi-log scale) against nominal time post-dose.
  - mean concentrations time plots (semi-log scale) against nominal time post-dose.
  - individual concentration time plots by participant (on semi-log scale) against actual time post-dose (there will be separate plots for each participant per scale).

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long the respective PK concentration is quantifiable in the matrix. For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

If data permits, non-compartmental PK parameters may be derived from the PF-06823859 serum concentrations.

Population PK modeling may be performed with the concentration data from this study alone or combined with data from other studies. In addition, a relationship between exposures and efficacy/safety endpoints may be evaluated using population PK/PD approach. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

6.3.2. PD Endpoints, including Selected Biomarkers (hsCRP, total IFNβ)

- Analysis population: biomarker analysis population.
- Analysis time points: all visits with samples taken.
- Analysis methodology: summary statistics. The change from baseline may also be investigated by applying the LANCOVA model (as described in Section 5.2.1). The

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log-transformation of the outcomes may be applied to the original observations after analysis of the distribution of observed data.

- Descriptive statistics for absolute values, change from baseline, percent change from baseline will include sample size, mean, standard deviation, median, minimum and maximum by visit.

- Presentations for biomarker concentrations will also include:

  - A listing of all concentrations sorted by participant ID, cohort, and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

  - A summary of concentrations by nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, CV, minimum, maximum and the number of concentrations above the lower limit of quantification.

  - Median concentrations time plots (semi-log scale) against nominal time post-dose.

  - Mean concentrations time plots (semi-log scale) against nominal time post-dose.

  - Individual concentration time plots by participant (semi-log scales) against actual time post-dose will be presented.

Additional biomarkers may be reported an additional exploratory analysis report.

6.3.3. Immunogenicity

Immunogenicity will be assessed through analysis of ADAs and NAbs.

- Analysis population: immunogenicity assessment population.

- Analysis time points: all visits with samples taken.

- Analysis methodology: summary statistics.

- Reporting results: The incidence of development of ADA NAb against PF-06823859 will be presented. Presentations for immunogenicity will include:

  - Summary of ADA and Nab analysis by sample and participant;

  - Summary of cumulative incidence of ADA and NAb over time;

  - Summary of ADA and NAb incidence and titers over time;

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- Summary of time to first ADA and NAb occurrence;
- Impact of ADA and NAb status of PF-06823859 concentrations (data permitting);
- Impact of ADA and NAb status on biomarkers (data permitting);
- Impact of ADA and NAb status on CDASI (data permitting);
- Combined plot of PK, PD (total IFNβ), ADA and NAb response over time (data permitting).

6.3.4. C-SSRS

For each of the observation times the descriptive statistics will show number of participants in the data set and proportion of participants who completed sucide, attempted suicide had preparatory acts towards imminent suicide behavior, suicideal ideation or self-injurious behavior without suicidal attempt in both cohorts.

6.3.5. PROs (EQ-5D-5L, SF-36 v2 acute)

- Analysis population: Skin analysis set and muscle analysis set.
- Analysis time points: all visits with responses assessed.
- Analysis methodology: summary statistics. For the SF-36 observations, two summary component scores (PCS and MCS) and 8 scale subscores (PF, RP, BP, GH, VT, SF, RE, and MH) will be summarized. CFB will also be reported for the PCS and MCS scores. For the EQ-5D-5L, the summed number of checked boxes under each of the five sections will be reported.
- Reporting results:
  - Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum by visit.
  - Absolute values: The sample size, mean, standard deviation, median, minimum and maximum by visit.

Ad-hoc analyses for PROs with minimum clinically important differences may be performed.

6.4. Subset Analyses

No subset analyses are planned.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

A breakdown of all participants will be provided by demographic characteristics (age, race, weight, body mass index, and height), extent of disease and prior use of conventional therapy in accordance with Pfizer data standards. Mean steroid use and duration of disease will also be presented by cohort. Baseline CDASI (activity and damage) will be summarized descriptively.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition and will show which participants were analyzed in the full analysis set, skin analysis set, and muscle analysis set, and as well as for safety, PK and PD. Frequency counts will be supplied for participant discontinuations by treatment. Disposition will also be summarized separately for participants who discontinue.

Data will be reported in accordance with reporting standards.

6.5.3. Study Treatment Exposure

The number of the doses of active treatment will be recorded and summarized by cohort.

6.5.4. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings. These will be listed for each cohort and cohort will be indicated. A separate listing may be provided for DM-related prior and concomitant medications.

6.6. Safety Summaries and Analyses

The safety will be monitored over the study period that includes treatment and follow-up periods in all cohorts.

6.6.1. Adverse Events

Overall standard AE endpoints for this study are incidence of TEAE, incidence of SAEs, and incidence of AEs leading to discontinuation. Separate AE tables will show the AE data for each cohort.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. The laboratory data listing will indicate cohort.

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6.6.3. Vital Signs

Systolic blood pressure, diastolic blood pressure and pulse rate will be listed and tabulated by week with descriptive statistics (N, mean, standard deviation, median, minimum and maximum). Change from baseline (defined as mean pre-dose value collected at baseline will also be summarized using the same descriptive statistics by week.

6.6.4. Electrocardiograms

Single 12-lead ECGs should be collected at times specified in the Schedule of Activities.

The following ECG data will be listed: QT, QTc (Fridericia's), heart rate, QRS duration, PR interval. QTc based on Fridericia's correction will be derived.

Baseline and change from baseline for QT, QTcF, heart rate, QRS, PR will be summarized using descriptive statistics by study week in each cohort. For QTcF a classification of absolute values and increase from baseline will be used.

The numbers of subjects with ECG outcomes within the specified categories (see Section 9.4) and number of participants with uncorrected QT values ≥500 ms will be summarized by treatment and study week.

6.6.5. Physical Examination

All physical exam data will be provided in the listings.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessments, facilitating PK/PD modeling, and/or supporting clinical development.

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8. REFERENCES

1. Aggarwal R, Rider LG, Ruperto N, et al. 2016 American college of rheumatology/European league against rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: an international myositis assessment and clinical studies group/paediatric rheumatology international trials organisation collaborative initiative. Arthritis & Rheumatology. 2017;69(5):898-910.

2. Pfizer Guidance for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018.

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9. APPENDICES

9.1. Definition and Use of Visit Windows in Reporting

The currently assumed assignment of the observations to visits is based on the participant's arrival day. It assumes that the arrival times for postbaseline visits occur within the (-3,3) days time window centered around the target day as specified in the schedule of activities. We will check the validity of the assumption by the analysis of distributions of actually observed arrival days at the end of the study and may update the assignment rules slightly.

Visit Label	Targeted Day	Analysis window
Baseline*	Day 1 (reference day)	Day 1 (reference day)
Week 4	Day 29	Days 26-32
Week 8	Day 57	Days 54-60
Week 12	Day 85	Days 82-88
Week 16	Day 113	Days 110-116
Week 20	Day 141	Days 138-144
Week 24	Day 169	Days 166-172
Week 28	Day 197	Days 194-200
Week 32	Day 225	Days 222-228
Week 36	Day 253	Days 250-256
Week 40	Day 281	Days 278-284
Week 44	Day 309	Days 306-312
Week 48	Day 337	Days 334-340
Week 52	Day 365	Days 362-368
Week 56	Day 393	Days 390-396
Week 60	Day 421	Days 418-424
Week 64	Day 449	Days 446-452
Week 68	Day 477	Days 474-480

*Baseline occurs within 7 days of Week 24 C0251002 Day 1.

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If more than one observation from the same participant falls into the same window then the association of the observation with the visit will be done after the consultation with the study clinician and lead statistician.

9.2. CDASI

Figure 2. Presents the CDASI Scale

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The main outcomes of interest are the activity score and damage score.

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9.2.1. The Activity Score (AS)

The Activity Score (AS) is calculated as a sum of the contribution from the extent score (ES), Gottorn hands score (GHS), peringual score (PS) and allopecia score (AS).

$$AS = ES+GHS +PS+AS$$

The total extent score (ES) is obtained by summing up scores for the total erythema (ER, quantifies redness of the skin or mucous membranes), total scaling (SC, quantifies peeling of the skin) and total erosion/ulceration (EU, quantifies presence of the deeper wound).

$$ES = ER+SC+EU$$

Total erythema (ER), scaling (SC) and erosion/ulceration (EU) scores are calculated as a sum of the contributions from 15 individual areas of the body. The range of the total erytherma score is 0-45, the range of the total scaling score is 0-30 and the range of total erosion/ulceration is 0-15. The resulting range of the extent score is 0-90.

Gottorn hands score (GHS) characterizes papules (swellings) on hand and is a sum of the papule's characterization score (range 0-6) and ulceration score (range = 0-1).

Peringual score (PS) characterizes abnormalities around nails and its range is 0-2. The alopecia score (AS) characterizes hair loss and has the range 0-1.

The resulting range of the activity score is 0-100.

9.2.2. Damage Score

The Damage Score (DS) is calculated as a sum of the total poilkiloderma score (POLS), total calcinosis score (CALS) and Gotorn's hands damage score (GHDS).

$$DS = POLS +CALS+GDHS$$

The polikiolderma score characterizes specific dispigmentation in the particulal area and calcinosis score characterizes calcification of the skin in the particular area. The total polikiolderma score (POLS) and the total calcinosis score (CALS) are summed up over 15 individual areas in the body and each of them has range 0-15. The Gotorn's hands damage score (GHDS) has the range 0-2 so that the damage score (DS) has the range 0-32.

In our analysis we will look at the activity score (AS), damage score (DS).

For the activity score we will analyze the following subscores: total extent score (ES), total erythema score (ER), total scaling (SC) and total erosion/ulceration scores (EU), Gottorn hands score (GHS), peringual score (PS), and alopecia score (AS).

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For the damage score we will analyze the following subscores: total poilkiloderma score (POLS), total calcinosis score (CALS) and Gotorn's hands damage score (GHDS).

9.3. TIS using CSM in DM

The total improvement score is the sum of all 6 improvement scores associated with the change in each core set measure. A total improvement score of ≥20 represents minimal improvement, a score of ≥40 represents moderate improvement, and a score of ≥60 represents major improvement.[1]

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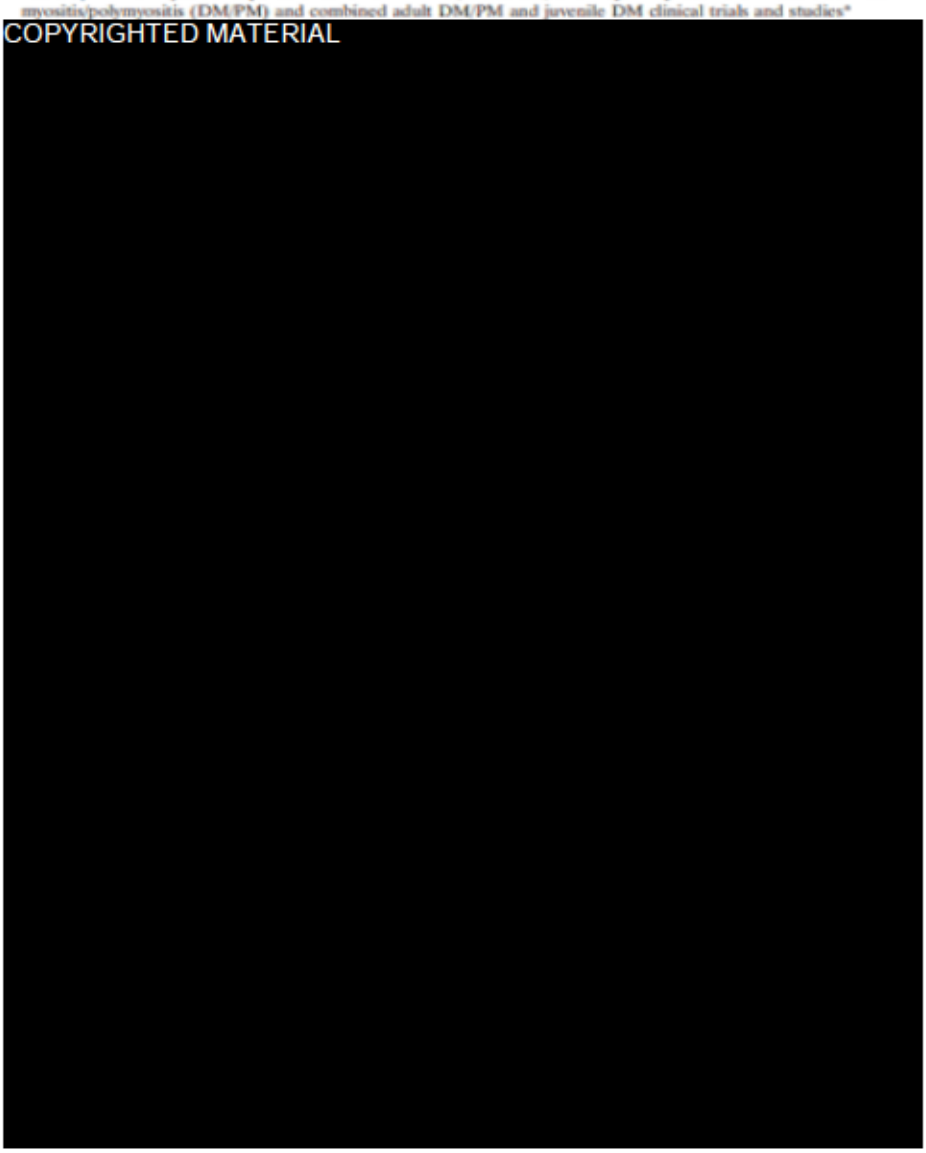
ACR/EULAR CRITERIA FOR CLINICAL RESPONSE IN ADULT DERMATOMYOSITIS AND POLYMYOSITIS

Table 3, Final myositis response criteria for minimal, moderate, and major improvement in adult dermatomyositis/polymyositis (DM/PM) and combined adult DM/PM and juvenile DM clinical trials and studies*



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9.4. Categories for ECG and Vital Sign Outcomes

The following Pfizer's standard will be used. For the sitting measurements of pulse rate the categories for the supine pulse rate (min <40 bpm and max >120 bpm) will be used.

Categories for QTcF

QTcF (msec)	450< max. <480	480< max.<500	max. ≥500
QTcF (msec) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (msec)	max. ≥300	
PR (msec) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (msec)	max. ≥200	
QRS (msec) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

Measurements that fulfill these criteria are to be listed in the study report.

9.5. List of Abbreviations

Abbreviation	Term
Abs	absolute
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward

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Abbreviation	Term
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CDASI	cutaneous dermatomyositis disease area and severity index
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSM	core set measure
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EQ-5D-5L	EuroQoL 5 dimensions 5 levels
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAQ-DI	health assessment questionnaire disability index
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MDAAT	myositis disease activity assessment tool
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures

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Abbreviation	Term
MMT	manual muscle testing
MNAR	missing not at random
N/A	not applicable
NAb	neutralizing antibody
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PhGA	physician global assessement
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
PtGA	patient global assessment
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF	short form
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
TIS	total improvement score
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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