Protocol C3941003

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL COHORT STUDY TO EVALUATE THE SAFETY, TOLERABILITY, SKIN IRRITATION POTENTIAL AND PHARMACOKINETICS OF MULTIPLE-DOSE, TOPICAL ADMINISTRATION OF PF-07038124 TO JAPANESE HEALTHY PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 21 Sep 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 10 Mar 2021	Original 08 Jan 2021	N/A	N/A
2 21 Sep 2021	Amendment 1 12 Mar 2021	Clarification and addition of analyses	• Added plots of vital signs data (section 6.1.3) • Added plots of ECG data (section 6.1.4) • Clarified analyses of skin irritation assessment (section 6.1.5) • [redacted] • Added categorical class for QT of potential clinical concern to align with section 6.1.4 (appendix 1)

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3941003. 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

The followings are objectives and endpoints in this study. Estimand framework is not applied to this phase 1 study.

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety, tolerability, and skin irritation potential of PF-07038124, following multiple doses applied topically, in Japanese healthy participants.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests during the entire study. • Incidence and severity of local skin irritation at times indicated in SoA.

Secondary: • To characterize the PK of PF-07038124, following topical administration, in Japanese healthy participants.	**Secondary:** • PF-07038124 PK parameters following topical application on Days 1 and 10, as data permit: AUC_{tau}, and C_{max}, if applicable.
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[redacted]	[redacted]

2.1.1. Primary Estimand(s)

Not applicable.

2.1.2. Secondary Estimand(s)

Not applicable.

2.1.3. Additional Estimand(s)

Not applicable.

2.2. Study Design

This is a Phase 1, randomized, double-blind, vehicle-controlled, parallel cohort study to evaluate the safety, tolerability, skin irritation potential, and PK of PF-07038124 in Japanese healthy adult participants. Both cohorts can be conducted simultaneously.

This study will evaluate the safety, tolerability, skin irritation potential and PK following application of PF-07038124 at 0.01% concentration and vehicle to 2000 cm^2 (Cohort 1; approximately 10% BSA) or 4000 cm^2 (Cohort 2; approximately 20% BSA).

Participants will be randomized to receive PF-07038124 or vehicle in a ratio of 4 PF-07038124: 2 vehicle, per cohort. Each participant will receive multiple doses of PF-07038124 or vehicle starting on Day 1 topically applied for 10 consecutive days; applied QD in the AM for Cohort 1 and Cohort 2. Participants will not be randomly assigned to cohort. The first group of participants will be enrolled Cohort 1 followed by Cohort 2. All participants will have the study interventions randomly assigned, for the purpose of determining skin irritation potential, as well as PK, safety and tolerability. Dermal reactions at the application site will be assessed clinically using a visual grade that rates the degree of erythema, edema, and other signs of skin irritation.

The total participation time for each participant is approximately 66 days, including the screening period of up to 28 days, the double-blind treatment period of 10 days, and the follow-up period of 28 days from last dose of the study intervention.

Approximately 12 Japanese healthy adult participants are planned to participate in this study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Primary endpoints are:

- Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests during the entire study;
- Incidence and severity of local skin irritation at times indicated in SoA.

3.2. Secondary Endpoint(s)

Secondary endpoints are:

- PF-07038124 PK parameters following topical application on Days 1 and 10, as data permit: AUC_{tau}, and C_{max}, if applicable.

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3.4. Baseline Variables

There are no baseline variables used as covariates or stratification factors in this study.

The demographic and baseline characteristics data will include age, sex, ethnicity, race, weight, height, body mass index. Baseline variables are those collected on Day 1 prior to dosing or last measurement during screening visits before Day 1.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time.

The effective duration of treatment is determined by the lag time. The CDISC and Pfizer Standard (CaPS) default treatment LAG of 365 days post last dose of study drug will be used for this study.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last predose measurement.

3.5.3. Vital Signs

Supine blood pressure and pulse measurements will be taken at all time points listed in the Schedule of Activities given in the protocol.

Baseline will be defined as the last predose recording.

The following vital signs endpoints will be determined:

- The maximum decrease and increase from baseline over all measurements taken postdose for supine systolic and diastolic blood pressures;
- The maximum decrease and increase from baseline over all measurements taken postdose for supine pulse rate.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the treatment period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the change from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.5.4. Electrocardiograms

Standard 12-lead ECGs will be taken at all time points listed in the Schedule of Activities given in the protocol.

Baseline will be defined as the single supine 12-lead ECGs predose recording.

The QT, QTcF, PR, QRS and heart rate will be recorded at each assessment time.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where } RR = 60/HR \text{ (if not provided)}$$

The maximum absolute value (postdose) and the maximum increase from baseline will be determined over all measurements taken postdose for QTcF, QT, heart rate, PR and QRS.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the treatment period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.5.5. Skin Irritation Assessment

Local toleration will be assessed by Draize scoring and clinical observation in Table 2.

All numerical, letter grades, and superficial observations will be collected on the designated CRF.

Table 2. Skin Irritation Assessment Using Draize Scoring

Definition	Score
No reaction visible	0
Trace reaction – barely perceptible pinkness	1
Mild reaction – readily visible pinkness	2
Moderate reaction – definite redness	3
Strong to severe reaction – very intense redness	4

Definition of letter grades appended to a numerical grade:

J	Burning, stinging, itching
E	Edema – swelling, spongy feeling when palpated
P	Papules – red, solid, pinpoint elevations, granular feeling
V	Vesicles – small elevation containing serous fluid (blister-like), diameter 5 mm or less
B	Bulla reaction – fluid-filled lesion greater than 0.5 cm in diameter
S	Spreading – evidence of the reaction beyond the test site
W	Weeping – result of a vesicular or bulla reaction – serous exudates – clear fluid oozing or covering test area
I	Induration – solid, elevated, hardened, thickening skin reaction
XC	Additional comments appear in Comments section

Definition of superficial observations appended to a numerical and/or letter grade:

G	Glazing
Y	Peeling
C	Scab, dried film of serous exudates of vesicular or bulla reaction
D	Hyperpigmentation (reddish-brown discoloration of test area)
H	Hypopigmentation (loss of visible pigmentation at test area)
F	Fissuring – grooves in the superficial layers of the skin to glistening
R	Erosion(s)
U	Ulceration(s)
K	Scaling – flaking of skin

3.5.6. Other Safety Data

Additional safety data, body temperature, fibrinogen and hsCRP will be colledted as described in the protocol and will be listed (if collected in the sponsor's database).

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 unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration	All participants randomly assigned to study intervention who received a dose of PF-07038124 and in whom at least 1 plasma sample concentration value is reported.
PK parameter	All participants randomly assigned to study intervention who received a dose of PF-07038124 and who have at least 1 of the PK parameters of interest calculated.

5. GENERAL METHODOLOGY AND CONVENTIONS

This is a double-blind study. Final analysis will follow the official database release.

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or decision rules.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Binary endpoints will be summarized by treatment and visit (if appropriate) with number and percentage of participants in each category, if not otherwise specified.

5.2.2. Analyses for Continuous Endpoints

Continuous endpoints will be summarized by treatment and visit (if appropriate) using descriptive statistics, including n, arithmetic mean, median, standard deviation (SD), minimum and maximum will be used to summarize the endpoints, if not otherwise specified.

5.2.3. Analyses for Categorical Endpoints

Categorical endpoints will be summarized by treatment and visit (if appropriate) with number and percent of participants in the treatment group within each category, if not otherwise specified.

5.2.4. Analyses for Time-to-Event Endpoints

There are no time-to-event endpoints in this study.

5.3. Methods to Manage Missing Data

5.3.1. Standard Safety Data

For the analysis of standard safety data (i.e., all safety data except local skin irritation), the sponsor data standard rules for imputation will be applied.

5.3.2. Skin Irritation Assessment

Missing values will not be imputed.

5.3.3. Pharmacokinetic Data

Concentration Below the Limit of Quantification

In all data presentations (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 quantification.)

Deviations, Missing Concentrations and Anomalous Values

In summary tables, plots of mean profiles and plots of median profiles, summary statistics will be calculated setting concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% (>50%) of the data are missing.

Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event), this will be footnoted in summary tables and will not be included in the calculation of summary statistics.

6. ANALYSES AND SUMMARIES

All analyses described below will be conducted by treatment and cohort. In addition, data from vehicle in Cohort 1 and Cohort 2 will be pooled.

6.1. Primary Endpoint(s)

The primary endpoints of this study are the standard safety endpoints and local skin irritation presented in the Section 3.1. A set of summary tables split by cohort and treatment group (including pooled vehicle group) will be produced to evaluate potential risk associated with the safety and toleration of administering PF-07038124.

No formal analyses are planned safety data. The safety endpoints will be listed and summarized in accordance with the sponsor reporting standards, where the resulting data presentations will consist of participants from the safety analysis set.

6.1.1. Adverse Events

Adverse events will be listed and summarized in accordance with the sponsor reporting standards.

6.1.2. Laboratory Data

Laboratory data will be listed and summarized in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.5.2.

6.1.3. Vital Signs Data

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by cohort, treatment group and postdose timepoints, according to the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using separate lines for the 2 vehicles. Corresponding individual plots of change from baseline will also be produced for each cohort and treatment.

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment and cohort using categories as defined in Appendix 1. Numbers and percentages of participants meeting categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

If necessary, maximum increases or decreases in vital signs may be summarized in addition to the above.

6.1.4. Electrocardiograms

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by cohort, treatment group and postdose timepoints. Baseline is as defined in Section 3.5.4. Tables will be paged by parameter.

Mean changes from baseline in QT, heart rate, QTcF, PR and QRS will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using separate lines for the 2 vehicles. Corresponding individual plots of change from baseline will also be produced for each cohort and treatment.

Changes from baseline in QTcF will also be plotted separately against PF-07038124 concentrations. This will be a scatter plot for all observations where QTcF and PF-07038124 concentration are recorded. Vehicle data will also be included (with drug concentration set to zero). Data from all cohorts will be plotted on the same figure. Different symbols will be used for each treatment.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by cohort and treatment group:

Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

6.1.5. Skin Irritation Assessment

Draize numerical grades, letter grades and superficial observations will be summarized by visit and assessment location (i.e., back, leg, arm, abdomen and chest). If there are multiple observations of numerical score in an assessment location (e.g., right arm and left arm), maximum score regardless of body side and directionality will be used. Similarly, if there are multiple observations of letter grades or superficial observations, “Y” will be used in

preference to "N" for summarization. For numerical grades, the followings will also be summarized:

- Maximum score by visit, regardless of assessment location;
- Maximum score during the study, regardless of visit and assessment location.

6.2. Secondary Endpoint(s)

6.2.1. Pharmacokinetic Parameters

PK parameters (AUC_{tau} and C_{max}) will be listed, summarized and plotted for participants in the PK parameter analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.3. Each PK parameter will be summarized by day and treatment group, and will include the set of summary statistics as specified in the table below:

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{tau}, C_{max}	n, arithmetic mean, median, SD, minimum, maximum, percent coefficient of variation (%CV), geometric mean and geometric %CV

There will be one summary table presenting all PK parameters.

AUC_{tau} and C_{max} will be plotted against treatment group, and will include individual participant values and geometric means for each treatment group. The plots will be paged by day. Geometric means will have a different symbol than individual values. A footnote will be added to the plots to indicate that geometric means are presented.

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6.4. Subset Analyses

No subset analysis will be conducted for this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics (age, gender, race, ethnicity, weight, height and body mass index) collected prior to the first dose of the study drug will be summarized in accordance with the sponsor reporting standards.

6.5.2. Study Conduct and Participant Disposition

The following participant dispositions will be reported following the sponsor reporting standards:

- A summary of participant discontinuations up to the end of study;
- Summary of participant dispositions analysed for PK and safety;
- Summary of numbers of participant treated by treatment group.

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medications as well as nondrug treatments will be provided in the listings.

6.6. Safety Summaries and Analyses

The details of safety analyses are described in the Section 6.1.

7. INTERIM ANALYSES

No interim analyses are planned.

8. REFERENCES

None.

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

CATEGORIES FOR QT_CF

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

CATEGORIES FOR QT

QT (ms)	max. ≥500		

CATEGORIES FOR PR AND QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥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 report.