# Protocol C1131001

**PHASE 1, RANDOMIZED, MULTI-CENTER, DOUBLE-BLIND, SPONSOR OPEN, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06835375 IN SUBJECTS WITH SEROPOSITIVE SYSTEMIC LUPUS ERYTHEMATOSUS OR RHEUMATOID ARTHRITIS**

# Statistical Analysis Plan (SAP)

**Version:** 3.0

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## Revision History

| Version | Date | Author(s) | Summary of Changes/Comments |
|---|---|---|---|
| Version 1.0 | 25-May-2018 | PPD | Not applicable |
| Version 2.0 | 08-Oct-2021 | PPD | Section 2.3: Added mapping of the analyses required for evaluation of exploratory objectives to SAP and bSAP.<br>Section 6.3: Separated table for PK parameters into the separate tables for single dose and multiple doses phases of the trial.<br>Sections 6.4, 6.5: Updated mapping of endpoints to SAP and bSAP analyses.<br>Section 8.2.2: Separated table for PK parameters into the separate tables for single dose and multiple doses phases of the trial.<br>Section 8.2.3: Added description of pharmacodynamic analyses.<br>Section 8.3.4: Described additional analyses: mapping of toxicity to severity and search for adverse events that may be caused by the cytokine release syndrome. |
| Version 3.0 | 14-Jan-2022 | PPD | Section 6.6: Added plots for time to ADA/NAb detection, spaghetti plots of PK, CCI and PK concentration and parameter summary by ADA/NAb status.<br>Section 8.2.3: Removed semi-log scale plots for CFB outcomes; removed subject level plots for CCI |

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

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES



## APPENDICES




[redacted]

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

- Section 2.1
  - Added a description of the cohorts actually used, and the actual doses to the description of planned cohorts and doses.
- Section 2.3
  - Added mapping of the analyses required for evaluation of exploratory objectives to SAP and bSAP.
- Section 6.3
  - Separated table for PK parameters into the separate tables for single dose and multiple doses phases of the trial.
- Sections 6.4, 6.5
  - Updated mapping of endpoints to SAP and bSAP analyses.
- Section 6.6
  - Added plots for time to ADA/NAb detection, spaghetti plots of PK, CCI [redacted], and PK concentration and parameter summary by ADA/NAb status.
- Section 8.2.2
  - Separated table for PK parameters into the separate tables for single dose and multiple doses phases of the trial.
- Section 8.2.3
  - Added description of pharmacodynamic analyses.
  - Removed semi-log scale plots for CFB outcomes; removed subject level plots for CCI [redacted].
- Section 8.3.4
  - Described additional analyses: mapping of toxicity to severity and search for adverse events that may be caused by the cytokine release syndrome.

## 2. INTRODUCTION

PF-06835375 is a humanized, afucosyl immunoglobulin (Ig) G1 antibody against C-X-C chemokine receptor type 5 (CXCR5), a surface receptor that is expressed on B cells, *bona fide* follicular T helper (Tfh) cells, and circulating follicular T helper-like (cTfh) cells.

*The goal of this first in human (FIH) study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PF-06835375. In particular, PD characterization will include assessment of magnitude and duration of CXCR5-positive cell depletion and recovery. Inhibition of the humoral immune responses via PF-06835375-mediated depletion of CXCR5-positive cells offers the potential for clinical evaluation in a population of seropositive autoimmune participants. Consequently, a mixed population of seropositive SLE or RA participants will be enrolled into this study.*

## 2.1. Study Design

*This is a Phase 1, randomized, multi-center, double-blind, sponsor open, placebo-controlled, single and multiple dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06835375 in participants with seropositive SLE or RA. Both IV and SC routes of administration will be tested.*

*This study will include two parts: Part A, consisting of approximately eight single ascending dose (SAD) cohorts, and Part B, consisting of approximately 6 multiple ascending dose (MAD) cohorts. Cohorts in Part A will be initiated sequentially. Participants in Part B will receive two doses of investigational product (first dose on Day 1 and second dose on Day 29), and will be enrolled concurrently with Part A following the completion of the initial cohorts in Part A. Participants who are randomized in Part A will not be eligible to participate in Part B of this study.*

*The study includes a Screening visit to assess eligibility and subsequent visits for a minimum of 16 weeks. Participants who meet the end of study criteria will have one follow-up phone call visit which will represent the end of study visit (unless additional follow up is needed for safety reasons or unresolved AEs attributable to immunogenicity). Participants, who do not meet the criteria to leave the study at Week 16, will continue with clinic visits every four weeks until they meet these criteria. Overall, participants are expected to stay in the study approximately 6-12 months (including screening). Participants who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn subject.*

*Both SLE and RA participants will be enrolled into this study. Minimum disease activity (ie, SLEDAI-2K or DAS28 cutoffs) is not required for entry as inclusion criteria. All subjects in both Part A and B will be followed for a minimum of 16 weeks prior to being able to qualify for study completion based on the cellular recovery.*

*It is at the sponsor's discretion to dose escalate, to repeat the same dose, or to test a lower dose based on emerging data.*

*The PD effects of PF-06835375 on the immune system will be evaluated using multiple biomarkers, including extensive longitudinal flow cytometry assessment pre- and post-administration of IP* (investigational product). *In addition, the functional effects of PF-06835375 will be assessed with two vaccine challenges* CCI [redacted] CCI [redacted].

*Throughout the study, B cell counts obtained from a CLIA (Clinical Laboratory Improvement Amendments) certified central lab will be used for clinical decision making (inclusion/exclusion criteria, dose escalation, initiation of Part B and for the end of study criteria).*

Figure 1 (below) shows the study schematic and Table 1 shows the planned cohorts and actual dosing regimens Cohorts A7, A8, X6 were not used, the doses in both cohorts A6 and B4 were both reduced from 10 mg to 6 mg and the dose in cohort B5 was reduced from 30 mg to 10 mg.

**Figure 1. Study Schematic**

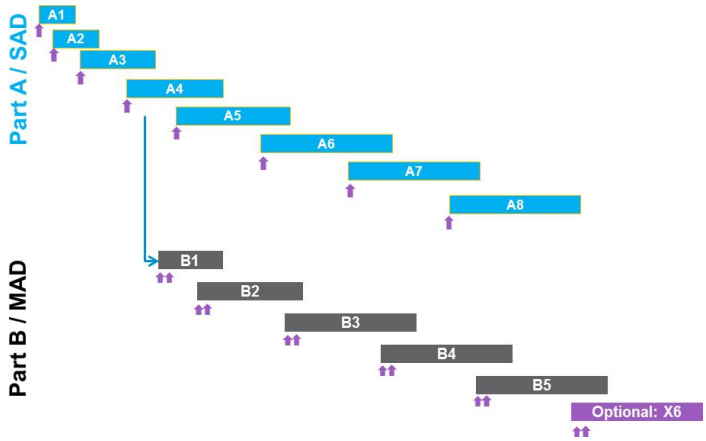

**Table 1. Planned Cohorts**

| *Cohort Name* | *Administration Route* | *Proposed Human Dose[a] (mg)* | *Actual dose (mg)* | *Expected Number of Participants Per Cohort[c]* |
|---|---|---|---|---|
| ***Part A (SAD)*** | | | | |
| *A1* | *IV* | *0.03* | *0.03* | *3a, 1p* |
| *A2* | *IV* | *0.1* | *0.1* | *3a, 1p* |
| *A3* | *IV* | *0.3* | *0.3* | *3a, 1p* |
| *A4* | *IV* | *1* | *1* | *3a, 1p* |
| *A5* | *IV* | *3* | *3* | *6a, 2p* |
| *A6* | *IV* | *10* | *6* | *6a, 2p* |
| *A7* | *IV* | *30* | *Not used* | *6a, 2p* |
| *A8* | *IV* | *100* | *Not used* | *6a, 2p* |
| ***Part B (MAD)*** | | | | |
| *B1* | *SC[b]* | *0.3* | *0.3* | *6a, 2p* |
| *B2* | *SC[b]* | *1* | *1* | *6a, 2p* |
| *B3* | *SC[b]* | *3* | *3* | *6a, 2p* |
| *B4* | *SC[b]* | *10* | *6* | *6a, 2p* |
| *B5* | *SC[b]* | *30* | *10 mg* | *6a, 2p* |
| *X6[d]* | *SC[b]* | *up to 30* | *Not used* | *Up to 24 total (16a, 8p)* |

*Abbreviations: a = active, p = placebo; IV = Intravenous; SC = subcutaneous*

a. *Doses may be changed based on available emerging safety, tolerability, PK and PD.*

b. *Route of administration may be changed based on available emerging safety, tolerability, PK and PD.*

c. *Sponsor may elect to add more subjects into the planned cohorts for any reason, including but not limited to eg, subject withdrawal, higher than expected PD effect, etc. The study will enroll up to a total of approximately 112 participants.*

d. *Optional cohort called "X".*

## 2.2. Study Objectives

### 2.2.1. Primary

- *To evaluate the safety and tolerability of single and multiple ascending intravenous (IV) and subcutaneous (SC) doses of PF-06835375 in participants with SLE and RA.*

### 2.2.2. Secondary

1. *To evaluate the effect of PF-06835375 on depletion of circulating CXCR5 positive B cells and cTfh cells in participants with SLE and RA.*

2. *To characterize pharmacokinetics (PK) profile of PF-06835375 in participants with SLE and RA.*

3. *To evaluate immunogenicity of PF-06835375 in participants with SLE and RA.*

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[redacted]

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[redacted]

## 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is a sponsor open study, with the investigator and subject blinded to study treatment. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/study staff until the conclusion of the study. Final analysis will follow the official database release.

Specific Pfizer personnel (clinician, statisticians, and clinical pharmacologists) will be un-blinded to subject treatment assignments in order to permit real-time interpretation of the pharmacokinetic, flow cytometry and safety data, and to provide information necessary to potentially alter the dose escalation sequence.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

No statistical hypotheses will be tested in this study.

### 4.2. Statistical Decision Rules

No statistical decision rules will be used for this study.

## 5. ANALYSIS SETS

### 5.1. Full Analysis Set

The full analysis set is comprised of all randomized participants.

## 5.2. Pharmacokinetic Analysis Sets

### 5.2.1. Concentration Analysis Set

*The PK concentration population is defined as all enrolled participants treated who have at least 1 concentration.*

### 5.2.2. Parameter Analysis Set

*The PK parameter analysis population is defined as all enrolled participants treated who have at least 1 of the PK parameters of interest.*

## 5.3. Pharmacodynamic Analysis Set

The pharmacodynamic analysis population is defined as all enrolled participants who receive at least 1 dose of study medication and have at least 1 pharmacodynamic measurement.

## 5.4. Safety Analysis Set

All participants who receive at least 1 dose of study medication will be included in the safety analyses and listings.

## 5.5. Other Analysis Sets

None.

## 5.6. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

## 5.7. Protocol Deviations

Participants who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

### 5.7.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess participants against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

### 5.7.2. Deviations Assessed Post-Randomization

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

## 6. ENDPOINTS AND COVARIATES

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### 6.2. Safety Endpoints

In this section, the safety endpoints that will be measured during the study are detailed. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *ECG results.*

### 6.2.1. Adverse Events

Any events occurring following start of treatment will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

### 6.2.2. Laboratory Safety Tests

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

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last pre-dose measurement (first treatment for MAD cohorts).

### 6.2.3. Vital Signs

Single sitting blood pressure, pulse measurements and temperature will be taken at times detailed in the Schedule of Activities given in the protocol.

The last pre-dose measurement at Day 1 will be used as the baseline. The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject 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 changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

### 6.2.4. ECG

A single 12-lead ECG will be obtained on all participants at screening and follow-up. *ECGs will be collected in triplicate in Part A on Days 1 and 2, in Part B on Days 1, 2 and 29. The Day 1 ECG values will serve as each subject's baseline values*

The QT, QTc, PR, RR, 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:

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

If not supplied, QTcB will be derived using Bazett's heart rate correction formula:

$$QTcB = QT / (RR)^{1/2} \qquad \text{where RR = 60/HR (if not provided)}$$

The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. Baseline will be defined as the average of the triplicate pre-dose recordings at Day 1.

The maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, QT, heart rate, PR and QRS, will be determined over the first 12 hours postdose for Day 1 and Day 29 (part B only) separately, and also over all measurements taken postdose for QTcF, PR and QRS.

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

### 6.2.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed as necessary.

## 6.3. Pharmacokinetic Endpoints

Blood samples for PK analysis of PF-06835375 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters that will be calculated for PF-06835375 (if possible) for PF-06835375 for Part A (see Table 2) and Part B (see Table 3) from the concentration-time values using standard non-compartmental methods.

**Table 2. Noncompartmental PK Parameters for Part A (Single Ascending Dose)**

| Parameter | Analysis Scale | PF-06835375 |
|---|---|---|
| $AUC_{672}$ | ln | D |
| $AUC_{last}$ | ln | D |
| CCI [redacted] | [redacted] | [redacted] |
| $AUC_{inf}$* | ln | D |
| $AUC_{inf}$(dn)* | ln | D |
| $C_{max}$ | ln | D |
| CCI [redacted] | [redacted] | [redacted] |
| $T_{max}$ | R | D |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

**Table 3. Noncompartmental PK Parameters for Part B (Multiple Ascending Dose)**

| Parameter | Dosing Day | Analysis scale | PF-06835375 |
|---|---|---|---|
| AUCτ | 1, 29 | ln | D |
| CCI | | | |
| | | | |
| $C_{av}$(dn) | 1, 29 | ln | D |
| AUClast | 1, 29 | ln | D |
| AUClast (dn) | 1, 29 | ln | D |
| $C_{max}$ | 1, 29 | ln | D |
| CCI | | | |
| $T_{max}$ | 1, 29 | R | D |
| CCI | | | |
| | | | |
| | | | |
| $C_{min}$ | 29 | ln | D |
| PTF | 29 | ln | D |
| $R_{ac}$ | 29 | ln | D |
| $R_{ac}$ $C_{max}$ | 29 | ln | D |

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

## 6.4. Pharmacodynamic (PD) Endpoints that Will be Addressed in SAP

Change from baseline will be explored for the concentrations of following biomarkers.

1. Circulating CXCR5 positive B cells, cTfh cells.

CCI

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CCI

CCI

### 6.7. Covariates

None.

## 7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

### 7.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings and PK analyses), concentrations below the limit of quantification (BLQ) will be set to LLOQ/2, where LLOQ denotes the lower limit of quantification. For the PK analyses the concentrations below the limit of quantification (BLQ) will be set to zero.

(In listings BLQ values will be reported as "<LLOQ", where LLOQ will be replaced with the value for the lower limit of quantification).

### 7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, 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% of the data are missing.

### 7.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject 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 subject has a known biased estimate of a PK parameter (due for example to deviation in dosing), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

## 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 8.1. Statistical Methods

As this is an exploratory study, no formal hypothesis testing will be performed.

### 8.2. Statistical Analyses

#### 8.2.1. Analysis of Efficacy Data

Standard descriptive summaries will be presented for SLEDAI-2K (SLE patients) and DAS28 (RA patients).

#### 8.2.2. Pharmacokinetic Analysis

To assess the pharmacokinetics of PF-06835375, the PK parameters detailed in Section 6.3 will be listed and summarized for participants in the PK analysis set (as defined in Section 5.2). Missing values will be handled as detailed in Section 7. Each PK parameter will be summarized by dose which will be performed separately for the SAD and MAD parts of the study. Each summary will include the set of of summary statistics as specified in the Table 4 for SAD and Table 5 for the MAD respectively.

**Table 4. PK Parameters to be Summarized Descriptively for Part A (Single Ascending Dose)**

| Parameter | Summary Statistics |
|---|---|
| $C_{max}$, CCI $AUC_{inf}$, $AUC_{inf}$(dn), $AUC_{last}$, $AUC_{last}$ (dn), $AUC_{672}$, CCI | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |
| CCI | |

**Table 5. PK Parameters to be Summarized Descriptively for Part B (Multiple Ascending Dose)**

| Parameter | Summary Statistics |
|---|---|
| $AUC_{\tau}$, CCI , $AUC_{last}$, CCI $AUC_{last}$(dn), CCI , $C_{max}$, CCI Cav (dn), $C_{min}$, CCI PTF, $R_{ac}$, $R_{ac}$ $C_{max}$ | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |
| CCI | |

There will be summary tables presenting all PK parameters. Visit will be included in the subheading of PK parameter summary table. PK parameters will be summarized descriptively by dose/treatment group in concordance with sponsor's reporting standard.

To assess the relationship between the PK parameters and dose, CCI $AUC_{last}$ (Part A only) and $C_{max}$ will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented and that data from both cohorts are presented on the plot.

Supporting data from the estimation of $t_{½}$ and $AUC_{inf}$ will be listed by analyte where applicable: terminal phase rate constant ($k_{el}$); goodness of fit statistic from the log-linear regression ($r^2$); the percent of $AUC_{inf}$ based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of $k_{el}$. This data may be included in the clinical study report.

Some presentations for PF-06835375 concentrations will include:

- A listing of all concentrations sorted by subject ID, treatment group, dose, day 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 treatment, dose, day and 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 of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time post first dose by treatment group and dose (all treatments on the same plot per scale, based on the summary of concentrations by treatment group, dose and time post dose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time post first dose by treatment group and dose (all treatments on the same plot per scale, based on the summary of concentrations by treatment group, dose and time postdose).

- Individual concentration time plots by treatment group and dose (on both linear and semi-log scales) against actual time post dose (there will be separate spaghetti plots for each dose per scale).

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time post first dose [there will be separate plots for each subject].

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 PF-06835375 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 subject plots by time, the actual PK sampling time will be used.

### 8.2.3. Pharmacodynamic Analysis

All of the PD endpoints described in the Section 6.4 will be summarized by dose at each time point presented in tabular form or graphically. The descriptive statistics will include standard summaries of absolute concentrations, changes from baseline and percentage change from baseline. The presentations of PD endpoints will include:

- Listing of B and TfH cells sorted by subject ID, treatment group, dose and visit.

- Summary of B and cTfh Cell Depletion Parameters (Mean maximum % decrease from baseline, Mean duration of depletion below 10 cells/µL after first dose) following Single Dose Intravenous Administration.

- Summary of B and cTfh Cell Depletion Parameters (Mean maximum % decrease from baseline, Mean duration of depletion below 10 cells/µL after first and second dose) following Multiple Dose Subcutaneous Administration.

[redacted]

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on follow-up duration of participants.

### 8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06835375.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 6.2 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of participants from the safety analysis set.

#### 8.3.1. Treatment and Disposition of Participants

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

#### 8.3.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, gender (at birth), weight, body mass index, height, and primary diagnosis (SLE or RA). Each will be summarized by treatment group in accordance with the sponsor reporting standards. Background medication data will be summarized for each of the treatment groups.

#### 8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

Data will be reported in accordance with the sponsor reporting standards.

### 8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards. Several minor ad-hoc adjustments and additions will be conducted.

In the case report forms (CRF) the infusion-related adverse effect was characterized by toxicity grade, instead of the conventional characterization of the AE by severity. The possible toxicity grades are 0,1,2,3,4. The values of toxicity grades = 0, 1, 2 will be mapped to the "mild" category of the AE severity score and values of the toxicity score equal to 3 and 4 will be mapped to the "moderate" and "severe" scores accordingly. The explanation of this mapping from toxicity to severity scale needs to be included into the footnote of the otherwise standard summaries of the adverse events.

Listings with the descriptions of infusion-related reactions (IRR) and injection site reactions (ISR) will be created (separately for all causalities and treatment related adverse events) with the description of individual adverse effects.

Similar listings describing subsets of all events of participants who had preferred term of a special interest that may suggest the occurrence of cytokine release syndrome, with start on Day 1-3 after dose 1 (IV or SC) or Day 1- 4 after dose 2 (SC) will be created (separately for all causalities and treatment related adverse events). The set of preferred term of interest will include tachycardia, hypotension, hypertension, chills, vomiting, nausea, headache, pyrexia, dizziness, and palpitations. The observation of a group of two or more events from this set within a short time window after the dosing will be viewed as a potential cytokine release syndrome event (PCRE). The tabulation showing total number of participants and number and percent of PCREs within each of the doses will be created. Note that this analysis is exploratory and the list of preferred terms may be modified if needed.

### 8.3.5. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.2.2.

### 8.3.6. Vital Signs Data

Absolute values and changes from baseline for systolic and diastolic blood pressure and pulse rate will be summarized by treatment group and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.3.

Mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose. 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 placebos. Corresponding individual plots of changes from baseline will also be produced for each treatment group.

For systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% confidence interval) and plotted (mean) for each treatment group, dose and time point (including baseline).

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose time points 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.

### 8.3.7. ECG Data

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment group, and time postdose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.4.

Mean changes from baseline in QT, heart rate and QTcF 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 placebos. Corresponding individual plots of changes from baseline will also be produced for each treatment group.

Changes from baseline in QTcF will also be plotted separately against drug concentrations. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment. There will be 1 plot for each cohort.

Maximum increase from baseline (0 to 12 hours) for QTcF, heart rate, QT, PR and QRS will be summarized by treatment group, according to sponsor reporting standards.

In addition for QTcF, heart rate and QT, the differences between each dose and placebo (dose – placebo) for each subject will be summarized and plotted (N, mean, 90% confidence interval) for each cohort, dose and timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment group using categories as defined in Appendix 1 (for QTc these correspond to ICH E14[1]). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of participants with any single post-dose value ≥500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

### 8.3.8. Other Safety Data

None.

### 8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

## 9. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

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

### Categories for QTcF

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

### 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.


[redacted]