Protocol B7801001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, FIRST-IN-HUMAN TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF PF-06755347 AFTER SINGLE ASCENDING INTRAVENOUS INFUSIONS TO HEALTHY ADULT SUBJECTS

Statistical Analysis Plan (SAP)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	July 10, 2017	PPD	Original

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

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06755347 is a recombinant human IgG1 multimeric Fc fusion protein which includes the IgG1 hinge region, the CH2, and CH3 domains, with a human IgG2 hinge domain fused onto the C terminus. The molecule is designed to form Fc multimers, in order to enhance avidity to Fcγ receptors (FcγRs).

The current study is the first clinical trial proposed with PF-06755347. It is designed to evaluate the safety, tolerability, pharmacokinetics (PK), as well as potential pharmacodynamic (PD) effect of PF-06755347 following single intravenous (IV) doses of PF-06755347 to healthy adult subjects.

2.1. Study Design

This is a Phase 1, randomized, double-blind (Investigator and subject-blind, sponsor-open), placebo-controlled, parallel, single-ascending dose study of PF-06755347 in healthy subjects, to be conducted at a Pfizer Clinical Research Unit (CRU) that is in very close proximity to a major medical center. Personnel, trained in advanced cardiac life support, emergency resuscitative equipment and the management of anaphylaxis, are immediately available to treat systemic reactions under the supervision of a physician. IV fluids, epinephrine, antihistamine and methylprednisolone will be available for immediate parenteral use in the event of an anaphylactic reaction. In addition, a dedicated ambulance will be present at the research unit during dosing to facilitate rapid transfer to the Emergency Department of a major medical center, if needed.

The study will include 8 planned cohorts, with a provisional ninth cohort optionally added to explore or enhance the understanding of the full dose range. An optional Japanese cohort (Cohort 10) is also included. The optional Cohort 9 and Cohort 10 may or may not be conducted pending evaluation of available safety and PK data from other cohorts and at the discretion of the Sponsor.

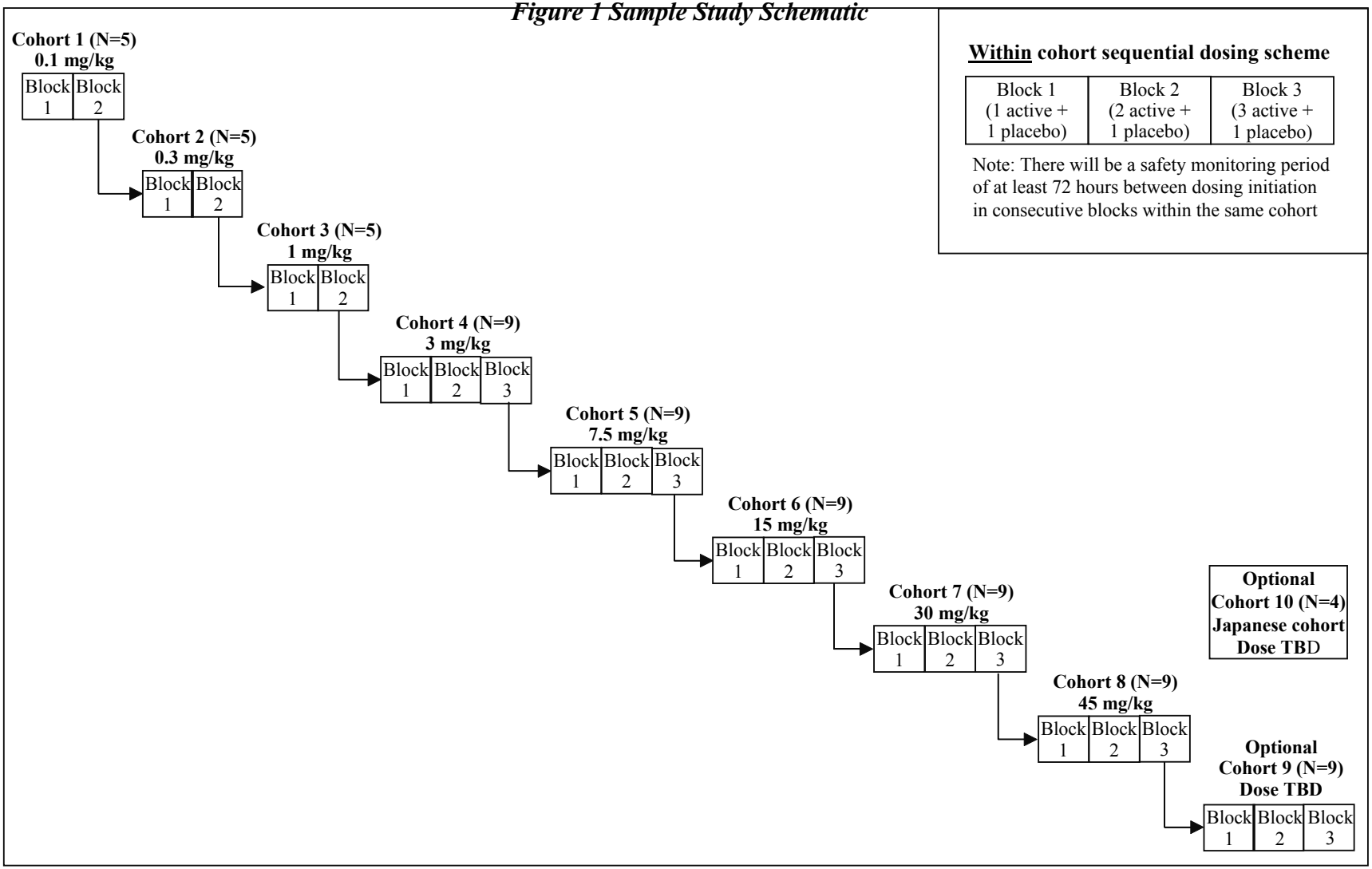
A total of approximately 73 healthy adult subjects are planned to be randomized. Fewer subjects (N=5, 3 active and 2 placebo) are planned for Cohorts 1-3, which are expected to have plasma exposure below the predicted efficacious concentration range (ie, doses ≤1 mg/kg). For Cohorts 4-9 with expected plasma exposure near or exceeding predicted efficacious concentration range (ie, doses >1 mg/kg), a total of 9 subjects (6 active and 3 placebo) is planned. If pharmacological activity or exposure is significantly greater than expected, the sample size for Cohorts 1-3 may be increased to 9 subjects at the discretion of the Sponsor in consultation with the PI. A total of 4 active subjects are planned for the optional Japanese cohort. A schematic of the overall study design is provided in Figure 1.

The subjects within each cohort (except for the Japanese cohort) will be dosed using a sentinel dosing strategy with sequential block design (diagramed in Figure 1). Each cohort will consist of 2 or 3 blocks, depending on the cohort sample size, with a monitoring period of at least72 hours between the dosing initiation in consecutive blocks. The number of subjects will increase sequentially, from 1 active and 1 placebo for the first block to 2 active and 1 placebo for the second block and 3 active and 1 placebo for the third block. For Cohorts 1-3, only the first and second blocks will be employed. The progression of dosing to the next block will occur if the dose is determined to be safe and well tolerated in the previous block by the PI. This sentinel dosing scheme will not be applied to the Japanese cohort, as the dose for this cohort, if conducted, will be a dose less than or equivalent to a dose studied in previous cohorts and deemed safe and well tolerated.

Screening evaluation will occur within 28 days prior to dosing. Eligible subjects who meet the entry criteria will be admitted into the CRU on Day -1 and are required to stay overnight through completion of Day 8 evaluations. Subjects will then return for outpatient visits per the Schedule of Activities through approximately Day 36 (≤1 mg/kg dose level) or Day 71 (>1 mg/kg dose level) for a total of approximately 5 or 10 weeks study participation. respectively from first dose to follow-up, excluding screening. The follow-up period may be extended for a cohort block if any subject in the particular cohort block tests positive for anti-drug antibody to PF-06755347 at the scheduled follow-up visit, or has detectable concentration of PF-06755347 at final follow-up visit.

If a subject discontinues during the trial, the subject may be replaced at the discretion of the Sponsor in consultation with the PI. Doses in the dose escalation sequence may be repeated or adjusted depending on the results obtained during the study to explore different doses and/or infusion/dosing rates as needed. The total number of cohorts including the optional Japanese cohort will not exceed 10.

Figure 1 Sample Study Schematic



2.2. Study Objectives

2.2.1. Primary Objectives

- *To evaluate safety and tolerability of single IV escalating doses of PF-06755347 in healthy adult subjects.*

2.2.2. Secondary Objectives

- *To characterize the plasma PK profile of PF-06755347 following single ascending IV infusions in healthy adult subjects.*

- *To evaluate the immunogenicity profile of PF-06755347 following single ascending IV infusions in healthy adult subjects.*

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- [redacted]

- [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Safety and pharmacokinetic (PK) data will be reviewed after each cohort.

This is a sponsor open study, with the investigators and subjects blinded to study treatment. Specific Pfizer personnel (e.g. analytical staff, medical monitor, clinician, statistician, and clinical pharmacologist) will be unblinded to subject treatments in order to permit real-time interpretation of the safety and pharmacokinetic data, and to provide information necessary to potentially alter the dose escalation sequence. 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. Unblinding will not be performed until the final database has been locked for all cohorts. Final analysis will follow the official database release.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Full Analysis Set

In general, the full analysis set is comprised of all randomized subjects. This population of subjects is not applicable for this study. Analysis sets for PK, safety and CCI data are defined in Sections 5.2, 5.4 and 5.5.

5.2. Pharmacokinetic Analysis Set

5.2.1. Concentration Analysis Set

The PK concentration population is defined as randomized subjects who received at least one dose and have at least 1 concentration.

5.2.2. Parameter Analysis Set

The PK parameter analysis population is defined as all randomized subjects who received at least one dose and have at least 1 of the PK parameters of interest.

5.3. Pharmacodynamic Analysis Set

The PD analysis population is defined as all randomized subjects treated who have at least one PD assessment in at least one cohort.

5.4. Safety Analysis Set

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

5.5. Other Analysis Sets

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5.6. Treatment Misallocations

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

If a subject takes a treatment that is not consistent with the treatment they are randomized to then they will be reported under the treatment that they actually receive for all safety, PK and CCI where applicable.

5.7. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg dosing error) 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 subjects 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

6.1. Efficacy Endpoint(s)

None.

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 and telemetry results.

6.2.1. Adverse Events

Any events occurring following start of treatment or increasing in severity 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 defined as the measurement on Day -1, or the last available pre-dose collection time point (whichever occurs later).

6.2.3. Vital Signs

Triplicate vital signs measurement will be taken at pre-dose only. Single supine blood pressure, oral temperature, and pulse rate measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

Baseline will be defined as the mean of the replicated pre-dose (0 hours) measurement on Day 1.

The following vital signs endpoints will be determined:

- Change from baseline in supine systolic and diastolic blood pressure, oral temperature and pulse rate.

- The maximum decrease and increase from baseline over all measurements taken post-dose for supine systolic and diastolic blood pressures, oral temperature and pulse rate.

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 and Telemetry

ECG

A single 12-lead ECG will be obtained on all subjects at screening and follow-up.

12-lead ECGs will be recorded in triplicate on all subjects at all other time points as detailed in the Schedule of Activities given in the protocol.

The QT, heart rate, QTcF, PR, RR and QRS 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 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 collected at 0 hours on Day 1.

The maximum absolute value (post-dose) and the maximum increase from baseline for QT, heart rate, QTcF, PR and QRS, will be determined over the first 24 hours post-dose for Day 1, and also over all measurements taken post-dose 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.

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will also be calculated.

Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythm of potential clinical concerns, which will document the time, duration and description of the clinically significant event.

6.2.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.3. Pharmacokinetic Endpoints

Blood samples for PK analysis of PF-06755347 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06755347 from the concentration-time values using standard non-compartmental methods:

Table 1. Non-compartmental PK Parameters

Parameter	Analysis Scale	PF-06755347
C_{max}	ln	D
C_{max} (dn)	ln	D
T_{max}	R	D
$t_{1/2}^{*}$	R	D
AUC_{last}	ln	D
AUC_{last} (dn)	ln	D
AUC_{inf}^{*}	ln	D
AUC_{inf}^{*} (dn)	ln	D
CL^{*}	ln	D
V_{ss}^{*}	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. PD Endpoints

None.

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6.6. Other Endpoints

6.6.1. Immunogenicity (ADA)

Response rates of the development of anti-PF-06755347 antibodies (ADA).

Definitions for positive ADA will be determined with the completion of the valdiation work for the assay and may be included in an amendment to this SAP prior to final database lock.

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), 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). For PK calculations, BLQ will be handled by the Pfizer standard processes.

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 an unexpected event such as dosing error), 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 CCI study, no formal hypothesis testing will be performed.

8.2. Statistical Analyses

8.2.1. Pharmacokinetic Analysis

To assess the pharmacokinetics of PF-06755347, the PK parameters detailed in Section 6.3 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5.2.2). Missing values will be handled as detailed in Section 7. Each PK parameter will be summarized by dose. Optional Cohort 10 Japanese (if applicable) will be analysed separately. Each summary will include the set of summary statistics as specified in Table 2.

Table 2. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, C_{max}(dn), AUC_{last}(dn), AUC_{inf}(dn), CL, V_{ss},	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be one summary table split by dose presenting all PK parameters.

To assess the relationship between the PK parameters and dose, dose normalized AUCinf (if data permit), AUC_{last} 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 separately. 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.

Supporting data from the estimation of t½ and AUC_{inf} will be listed 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}. These data may be included in the clinical study report.

Presentations for PF-06755347 concentrations will include:

- A listing of all concentrations sorted by subject ID, dose, 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 dose, cohort, 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-dose by dose and cohort (all doses on the same plot per scale, based on the summary of concentrations by dose, cohort and time post-dose).

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

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 PF-06755347 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.

Subjects having positive ADA may be analyzed separately to assess impact of ADA on PK concentrations and if no effect then those subjects will be included in the summarized PK concentration and parameter descriptive statistics. Refer to Section 8.3.8 for more details.

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-06755347. The optional Cohort 10 (if applicable) will be presented separately.

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 subjects from the safety analysis set (as defined in Section 5.4).

8.3.1. Treatment and Disposition of Subjects

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. Japanese subjects in Cohort 10 (if applicable) will be summarized separately from the subjects in other cohorts.

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

8.3.2. Demographic Data

A break down of demographic data will be provided for age, race, ethnicity, weight, body mass index and height. Each will be summarized by sex at birth and 'All Subjects' for each cohort separately and overall in accordance with the sponsor reporting standards.

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.

8.3.5. Laboratory Data

Laboratory data will be listed and summarized by treatment, which will be reported separately for Cohort 10 (if applicable) 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 in supine systolic and diastolic blood pressure, oral temperature, and pulse rate will be summarized by treatment and Cohort 10 (if applicable) in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, oral temperature, and pulse rate for each treatment will be plotted against time post-dose. On each plot there will be 1 line for each treatment, with separate plots Cohort 10 (if applicable). Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment , separately for Cohort 10 (if applicable), using categories as defined in Appendix 1. Numbers and percentages of subjects 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.

8.3.7. ECG and Telemetry Data

ECG

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment, which will be reported separately for Cohort 10 (if applicable) in accordance with the 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 post-dose. On each plot there will be 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

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 a separate plot for Cohort 10 (if applicable).

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by treatment, separately for Cohort 10 (if applicable) in accordance with the sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment, separately for Cohort 10 (if applicable), using categories as defined in Appendix 1 (for QTc these correspond to ICH E14[1]). Numbers and percentages of subjects 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 subjects with any single post-dose value ≥500 msec will also be produced for QTcF.

Telemetry

Telemetry data will be listed for those subjects with abnormal rhythms, showing the treatment, time, duration and description of the clinically significant event.

8.3.8. Other Safety Data

The percentage of subjects with positive ADA will be summarized by dose and presented separately for Cohort 10 (if applicable). For subjects with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The impact of ADA on PK and/or safety may also be assessed, if data permit.This may include:

- Spaghetti plots of individual PF-06755347 concentration time profile, grouped by ADA status, produced separately by treatment and for Cohort 10 (if applicable).
- Table summaries of PK parameters (AUC_{inf}, AUC_{last} and C_{max}) by ADA status, presented separately for Cohort 10 (if applicable).

8.3.9. Concomitant Treatments

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

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s) and FSH concentrations for all females of childbearing potential and urine drug screen will be obtained at Screening.

These data will not be brought in-house, and therefore will not be listed.

Any other screening data that is captured in the study database will be listed.

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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

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