Protocol C4541001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO CONTROLLED, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-07258669 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 01 Feb 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 01 Feb 2021	Amendment 1 09 Nov 2020	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4541001. 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.

Text in italics is taken directly from the protocol.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	*Endpoints*
Primary:	***Primary:***
• *To evaluate the safety and tolerability of single ascending doses of PF-07258669 administered orally to healthy adult participants.To evaluate the safety and tolerability of single ascending doses of PF-07258669 administered orally to healthy adult participants.*	• *Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, respiratory rate, oral body temperature, physical examinations, and neurological examinations.*
Secondary:	***Secondary:***
• *To evaluate the pharmacokinetics of PF-07258669 following single doses of PF-07258669 administered orally to healthy adult participants.*	• Pharmacokinetic (*PK*) *parameters derived from plasma PF-07258669 concentrations: Cmax, AUClast, AUCinf, Tmax, and t½, if data permit.*
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There are no estimands in this study.

2.2. Study Design

This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose study of PF-07258669 administered to healthy adult participants. Up to approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in this study. Each participant is planned to undergo 4 treatment periods receiving 3 doses of PF-07258669 and 1 dose of placebo.

Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

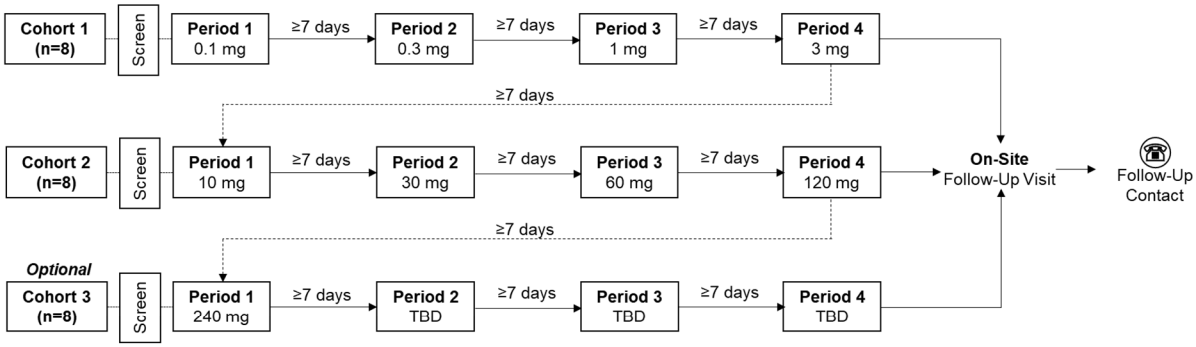
Dose levels will be escalated to bracket the expected clinical dose range, but projected exposures will not exceed the pre-defined human exposure limits. The optional third cohort will only be used if the objectives of the study are not fulfilled in Cohort 1 and Cohort 2. The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 14 weeks.

A starting dose of 0.1 mg of PF-07258669 is planned.

If a participant drops out before completing all study periods within a cohort, or withdraws for reasons unrelated to the safety of the study intervention, the participant may be replaced at the discretion of the investigator and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the investigator and sponsor.

Figure 1 shows the study design.

Figure 1: Study Schema



- Screening to dosing on Day 1 in Period 1: Maximum of 28 days for each cohort.
- Inpatient stay in each period: Day -1 to minimum of Day 3 (ie, 48 hours post-dose).
- In each period, 6 participants will be randomized to receive PF-07258669, and 2 participants will receive matching-placebo.
- Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.
- The starting dose level in Period 1 of Cohort 1 is 0.1 mg. All other planned dose levels in other periods and cohorts may be adjusted pending emerging safety, tolerability, and PK data from previous periods and cohorts.
- On-site follow-up visit to occur on Day 8 ±2 days in Period 4 only, with an additional follow-up contact occurring 28-35 days after administration of the final dose of study intervention.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoints are the following safety endpoints:

- Adverse events,
- clinical safety laboratory tests,
- vital signs,
- continuous cardiac monitoring,
- 12-lead electrocardiograms (ECG),
- respiratory rate,
- oral body temperature,
- physical examinations,
- neurological examinations.

3.1.1. Adverse Events

All adverse events that start, or worsen in severity, on or after the date and time of the first dose but before the follow-up contact (28-35 days after last dose) will be flagged as Treatment-Emergent Adverse Events (TEAEs).

TEAEs will be assigned to the dose taken in the period they start in. Events that occur during a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the most recent dose taken prior to the event.

3.1.2. Clinical Safety Laboratory Tests

Safety laboratory tests will be performed at the times specified in the Schedule of Activities in the protocol.

Baseline will be defined as the last non-missing pre-dose measurement for each period.

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

3.1.3. Vital Signs

Supine blood pressure (BP) and pulse rate measurements will be taken at the times specified in the Schedule of Activities in the protocol. Orthostatic BP and pulse rate measurements will also be taken at additional times specified in the Schedule of Activities in the protocol. Note that some of the supine BP and pulse rate measurements are collected as part of the orthostatic assessment.

Baseline will be the Pre-Dose (0 hour) assessment on Day 1 of each period.

The following endpoints will be determined:

- Postural differences (supine - standing) for systolic and diastolic BP (at each orthostatic assessment timepoint)
- Postural differences (standing – supine) for pulse rate (at each orthostatic assessment timepoint)
- Change from baseline in supine, standing and postural differences for systolic and diastolic BP and for pulse rate
- The minimum and maximum post-dose supine and standing for systolic and diastolic BP and for pulse rate
- The maximum post-dose postural differences for systolic and diastolic BP and for pulse rate
- The maximum decrease and increase from baseline over all measurements taken post-dose for supine, standing and postural differences for systolic and diastolic BP and pulse rate.

The maximum increase from baseline will be calculated by selecting the maximum change from baseline over the respective period, 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 changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.1.4. Continuous Cardiac Monitoring

Continuous cardiac monitoring will be performed using telemetry as outlined in the protocol.

All abnormal rhythms will be recorded and reviewed by the investigator for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. Events deemed of clinical concern will be recorded as AEs and will be summarized as part of the standard AE outputs.

3.1.5. 12-lead Electrocardiograms

A single 12-lead ECG will be obtained on all participants at screening. 12-lead ECGs will be recorded in triplicate on all participants at all other times detailed in the Schedule of Activities in the protocol.

The QT, QTcF, PR, RR, QRS complex and heart rate will be recorded at each assessment time. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

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

The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. Baseline will be the average of the triplicate ECG measurements collected at the pre-dose (0 hour) assessment on Day 1 of each period.

The following endpoints will be determined:

- Change from baseline in QT, QTcF, PR, QRS complex and heart rate
- The maximum post-dose QTcF, PR and QRS complex
- The maximum increase from baseline over all measurements taken post-dose for QTcF, PR and QRS values

The maximum increase from baseline will be calculated by selecting the maximum change from baseline over the respective period, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.1.6. Respiratory Rate

Respiratory rate will be measured at times specified in the Schedule of Activities in the protocol.

Baseline will be the Pre-Dose (0 hour) assessment on Day 1 of each period.

Change from baseline in respiratory rate will be determined, as well the maximum increase and decrease from baseline over all measurements taken post-dose.

3.1.7. Oral Body Temperature

Oral body temperature will be measured at times specified in the Schedule of Activities in the Protocol.

Baseline will be the Pre-Dose (0 hour) assessment on Day 1 of each period.

Change from baseline in body temperature will be determined, as well the maximum increase and decrease from baseline over all measurements taken post-dose.

3.1.8. Physical and Neurological Examination

Medical history, physical examination, and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

3.2. Secondary Endpoint(s)

The secondary endpoints are the following PK parameters, derived from the plasma PF-07258669 concentration-time profiles, if data permit, using standard non-compartmental methods and actual PK sampling times:

- C_{max},
- AUC_{last},
- AUC_{inf},
- T_{max},
- $t_{½}$.

Blood samples for PK analysis of plasma PF-07258669 will be collected according to the Schedule of Activities in the protocol.

Further definitions and details can be seen in Appendix 1.

Table 2 shows the analysis scale and method.

Table 2. Non-compartmental PK Parameters

Parameter	Analysis Scale	PF-07258669
AUC_{inf}*	ln	D
AUC_{last}	ln	D
C_{max}	ln	D
T_{max}	R	D
$t_{1/2}$*	R	D

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permit

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

For purposes of analysis, the following analysis sets are defined:

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.*
Evaluable	*All participants randomly assigned to study intervention and who receive a dose of study intervention.*
Safety	*All participants randomly assigned to study intervention and who receive a dose of study intervention. Participants will be analyzed according to the product they actually received.*

Participant Analysis Set	Description
PK Concentration	*All participants randomly assigned to study intervention and who receive a dose of study intervention and in whom at least 1 plasma concentration value is reported.*
PK Parameter	*All participants randomly assigned to study intervention and who receive a dose of study intervention and have at least 1 of the PK parameters of interest calculated.*

5. GENERAL METHODOLOGY AND CONVENTIONS

The analyses will be performed after database lock following dataset release after the last participant last visit.

5.1. Hypotheses and Decision Rules

There are no formal hypothesis tests planned for this study and no statistical decision rules will be applied.

5.2. General Methods

Unless specified otherwise, summaries will be produced by treatment.

5.2.1. Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

Log transformed continuous variables will be presented using summary statistics: number of observations, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.3. Methods to Manage Missing Data

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

5.3.1. Concentrations Below the Limit of Quantification

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

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

5.3.2. Deviations, Missing Concentrations and Anomalous Values

For PK CCI 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/statistician.

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

5.3.3. Pharmacokinetic CCI Parameters

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

If a PK CCI parameter cannot be derived from a participant'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 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 CCI parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For PK parameter calculations, the sponsor standard rules will be applied.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

Adverse events will be listed and summarized by treatment, in accordance with sponsor reporting standards using the safety population defined in Section 4.

6.1.2. Clinical Safety Laboratory Tests

Laboratory data will be listed and summarized by treatment, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.1.2.

6.1.3. Vital Signs

Absolute values and changes from baseline in supine, standing and postural changes for systolic and diastolic BP and pulse rate will be listed and summarized by treatment and timepoint,

according to sponsor reporting standards, using the safety population defined in Section 4. Tables will be paged by parameter. Baseline is as defined in Section 3.1.3.

Mean changes from baseline for supine, standing and postural changes for systolic and diastolic BP and pulse rate will be plotted against time post-dose. On each plot there will be one line for each treatment. Data from all cohorts will be plotted on the same figure using a single line for the pooled placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine and standing systolic and diastolic BP, maximum increase from baseline for standing and supine pulse rate, and maximum increase from baseline for postural differences (in systolic and diastolic BP, and pulse rate) will be summarized by treatment, according to sponsor reporting standards.

Maximum/minimum absolute values and changes from baseline for vital signs (for supine, standing and postural) will also be summarized descriptively by treatment using categories as defined in Appendix 2. 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.

6.1.4. Continuous Cardiac Monitoring

No summaries will be produced.

6.1.5. 12-lead Electrocardiagrams

Absolute values and *changes from baseline for the ECG parameters (ie, QT interval, heart rate, QTcF interval, PR interval, and QRS complex) will be* listed and *summarized by treatment and time*point according to sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.1.5.

Mean changes from baseline for QT, heart rate and QTcF will be plotted against time post-dose. On each plot there will be one line for each treatment. Data from all cohorts will be plotted on the same figure using a single line for the pooled placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum increase from baseline for QTcF will be summarized by treatment, according to sponsor reporting standards.

Absolute values and changes from baseline (QTcF, PR and QRS intervals) will also be summarized descriptively by treatment using categories as defined in Appendix 2 (for QTcF these correspond to ICH E14[1]). Numbers and percentages of participants meeting the categorical criteria will be provided.

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

When more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single

observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

Changes from baseline in QTcF will 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. *In addition, an attempt may be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship may be examined. The results of such analyses will not be included in the CSR.*

6.1.6. Respiratory Rate

Absolute values and changes from baseline in respiratory rate will be listed and summarized by treatment and timepoint, according to sponsor reporting standards, using the safety population defined in Section 4. Baseline is as defined in Section 3.1.6.

Mean changes from baseline will be plotted against time post-dose. On each plot there will be one line for each treatment. Data from all cohorts will be plotted on the same figure using a single line for the pooled placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum increase and decrease from baseline for respiratory rate will be summarized by treatment, according to sponsor reporting standards.

6.1.7. Oral Body Temperature

Absolute values and changes from baseline in oral body temperature will be listed and summarized by treatment and timepoint, according to sponsor reporting standards, using the safety population defined in Section 4. Baseline is as defined in Section 3.1.7.

Mean changes from baseline will be plotted against time post-dose. On each plot there will be one line for each treatment. Data from all cohorts will be plotted on the same figure using a single line for the pooled placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum increase and decrease from baseline for oral body temperature will be summarized by treatment, according to sponsor reporting standards.

6.2. Secondary Endpoint(s)

6.2.1. PK Parameters

Plasma concentrations of PF-07258669 will be listed and *summarized descriptively by dose and nominal PK sampling time* using the PK Concentration Analysis Set defined in Section 4. Presentations will include:

- a listing of all concentrations sorted by participant 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 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.
- individual concentration-time plots by dose (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).
- median concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).
- mean concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

The plasma PK parameters outlined in Section 3.2 *will be* listed and *summarized descriptively by dose in accordance with Pfizer data standards, as data permit*, using the PK Parameter Analysis Set defined in Section 4. Each PK parameter will be summarized by dose using the summary statistics as specified in the table below:

Table 4. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}	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 presenting all PK parameters. This will include data from all cohorts and will be presented by dose.

Supporting data from the estimation of t½ will be listed where applicable: terminal phase rate constant (kel); goodness of fit statistic from the log-linear regression (r2); the percent of AUCinf based on extrapolation (AUCextrap%); and the first, last, and number of time points used in the estimation of kel. These data may be included in the clinical study report.

Additional PK analyses may be performed if deemed appropriate, and may not be included in the CSR.

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6.4. Subset Analyses

No subset analyses are planned.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic data (age, biological sex, race, ethnicity, weight, body mass index and height) will be summarized by cohort and overall, in accordance with the sponsor reporting standards using the safety population defined in Section 4.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition and will additionally show the number and percentage of participants included in each analysis set defined in Section 4. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.3. Study Treatment Exposure

6.5.4. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s), as well as non-drug treatment(s), will be reported according to current sponsor reporting standards.

6.6. Safety Summaries and Analyses

See Section 6.1.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessments, facilitating dose-escalation decisions, facilitating PK modeling, and/or supporting clinical development.

8. REFERENCES

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

9. APPENDICES

Appendix 1. Pharmacokinetic Endpoints Derivations

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}*	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve • Only those data points judged to describe the terminal log-linear decline will be used in the regression
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*As data permit.

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>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	max. ≥160
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Systolic BP (mmHg) postural difference (supine – standing)	max. ≥20	
Diastolic BP (mm Hg)	min. <50	max. ≥90
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Diastolic BP (mmHg) postural difference (supine – standing)	max. ≥10	
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140
Pulse rate (bpm) postural difference (standing – supine)	max. ≥30	

Measurements that fulfill these criteria are to be listed.

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Appendix 4. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
CCI	[redacted]
BLQ	below the limit of quantitation
BP	blood pressure
C_{max}	maximum observed concentration
CCI	[redacted]
CRF	case report form
CSR	clinical study report
CCI	[redacted]
ECG	electrocardiogram
HR	heart rate
ICH	International Council for Harmonisation
LLQ	lower limit of quantitation
ln	natural log
N/A	not applicable
ND	not done
NS	no sample
NC	not calculated
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	PR interval
QRS	QRS interval
QTc	corrected QT interval
QTcF	corrected QT (Fridericia method) interval
R	raw (un-transformed)
RR	RR interval
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
T_{max}	time to maximum observed concentration
$t_{1/2}$	terminal half-life
TE	treatment-emergent
TEAE	treatment-emergent adverse event
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