Protocol C3421014

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-06882961 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 10 DEC 2020

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

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 10 Dec 2020	Original 5th Oct 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 C3421014. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***
Primary	***Primary***
To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.	*Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu as data permit.*
Secondary	***Secondary***
To evaluate the safety and tolerability of a single oral dose of PF-06882961 when administered to adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic impairment.	*Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.*
Tertiary/Exploratory	***Tertiary/Exploratory***
To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic impairment.	*Plasma: $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}/F$, T_{max}, $t_{1/2}$ as data permit.*

There are no estimands for this study.

2.2. Study Design

This is a non-randomized, open-label, single-dose, parallel-cohort, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of

[redacted]

[redacted]

PF-06882961 after a single, oral 20 mg dose administered in the fed state. A total of approximately 24 participants with varying degrees of hepatic function will be dosed in the study as shown in Table 2.

Table 2. ***Hepatic Function Categories Based on Child-Pugh Score***

Cohort	*Description*	*Child-Pugh Score*	*Number of Participants*
1	*Without hepatic impairment*	*Not Applicable*	*6*[a]
2	*Mild hepatic impairment*	*Class A (5 to 6 points)*	*6*
3	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*6*
4	*Severe hepatic impairment*	*Class C (10 to 15 points)*	*6*[b]

a. *Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when ≥75% of participants are dosed across the other 3 cohorts.*

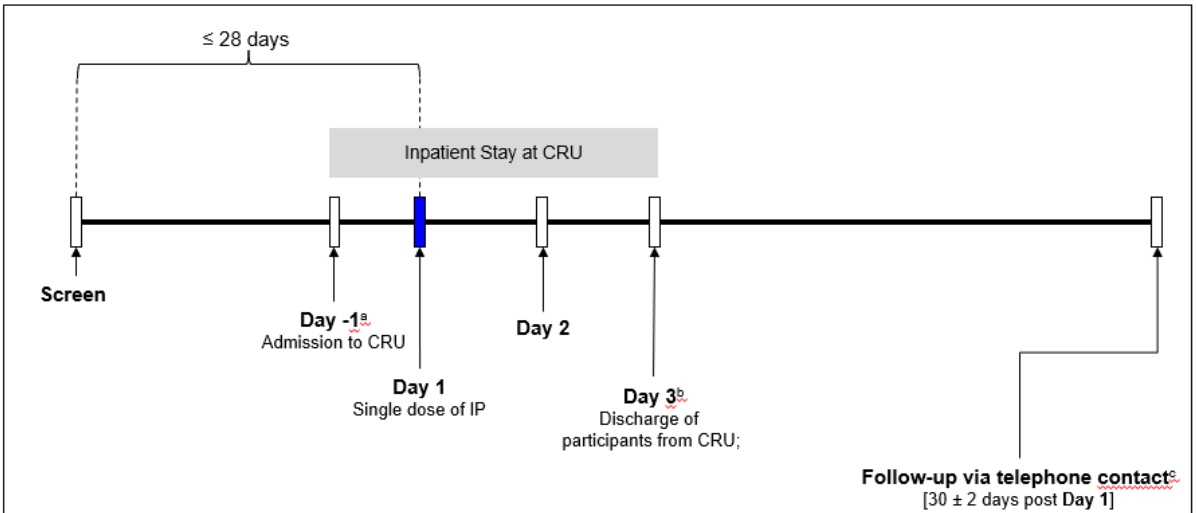
b. *If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.*

Categorization of participants into Cohort 2-4, inclusive, will be done based on Child-Pugh scores determined, as described in Appendix 8 (of the protocol) *at the screening visit. Participants will be dosed in a staged manner such that those with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first. Recruitment for participants with mild hepatic impairment (Cohort 2) will initiate when approximately 50% of the total participants in Cohorts 3 and 4 have been dosed. Participants without hepatic impairment (Cohort 1) will be recruited near the end of the study to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4.*

Participants who prematurely discontinue before completing all assessments may be replaced, at the discretion of the principal investigator (PI) and sponsor study team.

The overall study design is summarized in Figure 1.

Figure 1. Study Schema



a. Admission can occur at any time of day; once admitted, subject to be provided inpatient meal(s)
b. Following completion of procedures and morning meal, participants will be discharged from the CRU;
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion on Days 28 through 32

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Blood samples for PK analysis of PF-06882961 will be collected according to the Schedule of Activities given in the protocol.

PK parameters will be calculated (if possible) from the concentration-time data using standard non-compartmental methods.

3.1. Primary Endpoint(s)

- PF-06882961 Plasma Pharmacokinetic parameters: C_{max}, AUC_{inf}, AUC_{last}, fu as data permit.

The plasma PK parameters in Table 3 will be determined using standard non-compartmental methods:

Table 3. Summary of Plasma PK Parameters of PF-06882961 to be calculated

Parameter	Analysis Scale	PF-06882961 20mg
C_{max}	ln	A, D
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
fu	ln	A, D

*=if data permits. Abbreviations: A = analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 6 in Section 6.1.1.1; ln=natural-log transformed; R=raw (untransformed).

3.2. Secondary Endpoint(s)

- *Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.*

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

- the event starts during the effective duration of treatment (i.e. starting on or after the dose of PF-06882961 but before this dose plus lag time)

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time is attributed to the corresponding treatment. The lag time is defined by the Pfizer Standard of 365 days post last dose of IP.

A 3-tier approach for summarizing AEs will not be used due to the low number of participants planned to be recruited.

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.

For laboratory, vital signs and ECG data, baseline will be defined as the last pre-dose measurement on Day 1 or before.

3.3. Other Endpoint(s)

- Additional PF-06882961 Plasma Pharmacokinetic parameters: CL/F, V_z/F, T_{max}, $t_{1/2}$ as data permit.
- Unbound PF-06882961 Plasma Pharmacokinetic parameters: $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL_u/F, $V_{z,u}$/F as data permit.

The plasma PK parameters for PF-06882961 in Table 4 will be determined using standard non-compartmental methods:

Table 4. Summary of Additional Plasma PK parameters of PF-06882961 to be calculated

Parameter	Analysis Scale	PF-06882961 20mg

CL/F^*	ln	D
V_z/F^*	ln	D
T_{max}	R	D
$t_{1/2}^*$	R	D

*=if data permits. Abbreviations: D=displayed with descriptive statistics as outlined in Table 7 in Section 6.3; ln=natural-log transformed , R=raw (untransformed).

The plasma PK parameters for unbound PF-06882961 will be calculated as described in Table 5:

Table 5. Summary of Plasma PK parameters of Unbound PF-06882961 to be calculated

Parameter	Method of Determination	Analysis Scale	PF-06882961 20 mg
$AUC_{last,u}$	$fu \times AUC_{last}$	ln	D
$AUC_{inf,u}$*	$fu \times AUC_{inf}$	ln	D
$C_{max,u}$	$fu \times C_{max}$	ln	D
CL_u/F*	$Dose/(AUC_{inf,u})$	ln	D
$V_{z,u}/F$*	$Dose/(AUC_{inf,u} \times k_{el})$	ln	D

*=if data permits. Abbreviations: D=displayed with descriptive statistics as outlined in Table 7 in Section 6.3; ln=natural-log transformed , R=raw (untransformed).

3.4. Baseline Variables

Not Applicable.

3.5. Safety Endpoints

See Section 3.2.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.*
Evaluable	*All participants assigned to IP and who take at least 1 dose of IP.*
Safety	*All participants assigned to IP and who take at least 1 dose of IP.*

Participant Analysis Set	***Description***
PK Concentration Set	*The PK concentration population is defined as all participants who received at least 1 dose of PF-06882961 and in whom at least 1 plasma concentration value is reported.*
PK Parameter Set	*The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-06882961 and have at least 1 of the PK parameters of interest calculated.*

5. GENERAL METHODOLOGY AND CONVENTIONS

The following group labels (or similar) will be used for tables and figures unless otherwise stated:

Group	Description of Group	Label
1	Normal hepatic function	Without Hepatic Impairment
2	Mild hepatic impairment	Mild Hepatic Impairment
3	Moderate hepatic impairment	Moderate Hepatic Impairment
4	Severe hepatic impairment	Severe Hepatic Impairment

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

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.

5.2.2. Analyses for Categorical Endpoints

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

5.2.3. One-way Analysis of Variance (ANOVA)

The *one-way analysis of variance (ANOVA)* model will include group as a factor.

Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Example SAS code is given in Appendix 1.

Additionally, as an exploratory analysis, age and body weight may be explored as an additional covariate in the models, as appropriate. This will be implemented by utilizing a stepwise linear regression approach, with model selection using Akaike's Information

Criterion [AIC]). All the above covariates will be considered (group as a factor will be restricted to always remain in the model) and if the final model selected includes at least one of these additional covariates, this additional model will be reported in addition to the main ANOVA model above. Example SAS code is given in Appendix 1.

5.2.4. Linear Regression

Linear regression analysis will include hepatic function as a continuous explanatory variable (using continuous serum albumin, prothrombin time or total bilirubin, each modelled separately). *Estimates of the slope and intercept, together with a 90% CI, and the coefficient of determination (i.e. R-squared and adj-R-squared) will be obtained from the model.* Example SAS code is given in Appendix 1.

Additionally, as an exploratory analysis, age and body weight may be explored as an additional covariate in the models, as appropriate. This will be implemented by utilizing a stepwise linear regression approach, with model selection using Akaike's Information Criterion [AIC]). All the above covariates will be considered (hepatic function will be restricted to always remain in the model) and if the final model selected includes at least one of these additional covariates, this additional model will be reported in addition to the main linear regression above. Example SAS code is given in Appendix 1.

5.3. Methods to Manage Missing Data

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

In all PK 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.

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

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

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

Participants who experience events that may affect their PK profile (e.g. lack of compliance with dosing or vomiting) 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.

5.3.1. Plasma Pharmacokinetic Parameters

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

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

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment group/analyte with ≥3 evaluable measurements. For statistical analyses (i.e. mixed effect model), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a plasma PK 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.

6. ANALYSES AND SUMMARIES

Unless otherwise stated, all analyses, summaries and listings will be produced by group (as outlined in Section 5) which would include all 4 groups in the same analysis/output.

6.1. Primary Endpoint(s)

6.1.1. C_{max}, AUC_{inf}, AUC_{last}, fu for PF-06882961

6.1.1.1. Main Analysis

C_{max}, AUC_{inf} (if data permit), AUC_{last} and fu will be listed, summarized descriptively and analyzed by group for participants in the PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.1.

A one-way analysis of variance (ANOVA) described in Section 5.2.3, that includes all 4 groups in the same model, will be used to compare the natural log transformed of C_{max}, AUC_{inf}, AUC_{last} and fu of PF-06882961 separately, for each of the hepatic impairment groups (Test, Groups 2, 3, 4) to the healthy normal hepatic function group (Reference, Group 1).

For summary statistics and median or mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. The plasma PK parameters of PF-06882961 for each group will be summarized as specified in Table 6 below.

Table 6. Summary statistics to be produced for Plasma PK Parameters of PF-06882961

Parameter	Summary Statistics

C_{max}, AUC_{inf} (if data permit), AUC_{last} and fu	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

Supporting data from the estimation of $t_{1/2}$ will be listed by group: 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.

The following plot will be presented:

- Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, C_{max} and fu) will be constructed by group and overlaid with geometric means.

6.1.1.2. Exploratory/Supplementary Analysis

Exploratory analysis using linear regression will be used to analyze the potential relationship between appropriate PK parameters [eg, AUC_{inf}, AUC_{last}, C_{max} and fu] and hepatic function (eg, serum albumin concentration, prothrombin time or total bilirubin), as described in Section 5.2.3.

Plots of PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max} and fu) versus hepatic function (e.g. serum albumin, prothrombin time or total bilirubin, plotted separately) *will be constructed, with a regression line and 90% confidence region included* from the main linear regression model.

6.2. Secondary Endpoint(s)

Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described.

No formal analyses are planned for safety data.

The safety endpoints detailed in Section 3.2 will be listed and summarized in accordance with sponsor reporting standards based on the safety population (as defined in Section 4), with more details provided below.

6.2.1. Adverse Events

Adverse events will be summarised by group and overall, in accordance with sponsor reporting standards using the safety population defined in Section 4.

If applicable, subject discontinuations due to adverse events will be detailed and summarized.

6.2.2. Laboratory Data

Laboratory data will be listed and summarized by group and overall, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.2.

6.2.3. Vital Signs

Absolute values and changes from baseline in seated systolic and diastolic blood pressure and pulse rate will be summarised by group, according to sponsor reporting standards using the safety population defined in Section 4. Baseline is as defined in Section 3.2.

Maximum and minimum absolute values and maximum changes from baseline for seated vital signs will also be summarised descriptively by group 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 time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.2.4. ECG

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval and QRS interval will be summarised by group using sponsor reporting standards using the safety population defined in Section 4. Tables will be paged by parameter. Baseline is as defined in Section 3.2.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarised descriptively by group 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 time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.3. Other Endpoint(s)

6.3.1. Additional Plasma Pharmacokinetic Parameters of PF-06882961

$C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}/F$, T_{max}, $t_{1/2}$ will be listed and summarized descriptively by group in the PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

The additional plasma PK parameters of PF-06882961 for each group will be summarized as specified in Table 7 below.

Table 7. Summary statistics to be produced for Additional Plasma PK Parameters of PF-06882961

Parameter	Summary Statistics
$C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}/F$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
t½	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

The following plot will be presented:

[redacted]

[redacted]

- Box and whisker plots for individual PK parameters ($AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) will be constructed by group and overlaid with geometric means.

The following summaries will additionally be presented for the plasma concentration data of PF-06882961 using the PK Concentration Set (as defined in Section 4):

- a listing of all concentrations sorted by participant ID and nominal time post-dose for each group. 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 for each nominal time post-dose (produced separately for each group), 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 concentration time plots (on both linear and semi-log scales) against nominal time post-dose by group in the same plot.
- individual concentration time plots by group (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each group, with a line for each participant, per scale).

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.3.2. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses, but will not be analyzed specifically for this study and will not be included in the CSR.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

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

6.5.1. Baseline Summaries

Demographics data (age, biological sex, race, ethnicity, weight, body mass index and height) will be summarized by group and overall, as outlined in Sections 5.2.1 and 5.2.2 as applicable.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition by group and will show which participants were analyzed for pharmacokinetics and safety, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by group.

6.5.3. Concomitant Medications and Nondrug Treatments

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

6.5.4. Other Screening Data

These data will not be recorded in the study database, and therefore will not be listed.

6.6. Safety Summaries and Analyses

See Section 6.2.

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. Statistical Methodology Details

An example of SAS code for ANOVA:

```
proc mixed data = tab.pk;
        class group;
        model l&var = group /residual;
        lsmeans group/diff cl alpha=0.1;
        ods output lsmeans = lsmeans&var;
        ods output diffs=diffs&var;
run;
```

An example of SAS code for the PROC REG code for linear regression analyses:

```
proc reg data=tab.pk;
        model l&var=clcr/clb alpha=0.1;
        ods output ParameterEstimates = param&var;
        ods output FitStatistics = fit&var;
        ods output ANOVA = reg&var;
run;
```

An example of SAS code for stepwise regression with model selection using AIC:

```
proc glmselect data=tab.pk analysis plot=ALL;
    model pk_p = albumin age weight/ selection=stepwise (select = AIC stop = AIC)
        include=1 hierarchy=none showpvalues;
run;
```

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

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤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	
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 the report.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
Ae	Amount excreted
ANOVA	analysis of variance
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	maximum observed concentration
CSR	clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
IP	Investigational Product
LLQ	Lower limit of quantitation
Ln	Natural log
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
T_{max}	Time to maximum observed concentration
$t_{1/2}$	Half life
Vz/F	Apparent volume of distribution