Protocol B7921026

A PHASE 1, OPEN LABEL, FIXED SEQUENCE STUDY TO ESTIMATE THE EFFECT OF MULTIPLE DOSE PF-06650833 ON THE PHARMACOKINETICS OF SINGLE DOSE ORAL CONTRACEPTIVE STEROIDS IN HEALTHY FEMALE PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 1

Date: 27 Oct 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 27 Oct 2021	Original 29 Jul 2021	N/A	N/A

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

2. INTRODUCTION

This study will evaluate the effect of PF-06650833 on pharmacokinetics of oral contraceptive (OC) steroids, in order to select appropriate contraception requirements in Phase 2 studies.

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This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7921026. 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 estimate the effect of multiple oral doses of PF-06650833 on the PK of a single dose of a combination OC in healthy female participants.*	• *C_{max} and AUC_{last} of EE and LN.*
Secondary:	***Secondary:***
• *To evaluate the safety of PF-06650833 when co-administered with a single dose of a combination OC in healthy female participants.*	• *Safety: laboratory tests, AEs reporting and vital signs.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To characterize the PK of a single dose of a combination OC with or without PF-06650833 in healthy female participants.*	• *T_{max}, and if data permit CL/F, $t_{½}$ and AUC_{inf}, of EE and LN.*

2.2. Study Design

This is a Phase 1, fixed-sequence, multiple-dose, open-label study of the effect of multiple dose PF-06650833 on single dose OC PK in healthy female participants. A total of approximately 10 healthy female participants will be enrolled in the study. The study will consist of 2 periods in a single fixed sequence. Participants will be screened within 28 days of the first dose of investigational product in Period 1. Participants will report to the CRU the day prior to Day 1 dosing in Period 1. Participants will remain in the CRU for a total of 16 days and 15 nights. There will be no washout period.

On Period 1 Day 1, participants will be dosed with a single administration of OC in the form of 1 PORTIA® (EE and LN) or equivalent tablet, orally. OC (EE and LN) PK will then be assessed at pre-dose and over 48 hours, post OC dosing. Period 1 will be immediately followed by Period 2 with no washout, in which participants will be dosed orally with PF-06650833 400 mg MR QD for 9 days followed by administration of a single dose of OC on the morning of Day 10. OC PK will be assessed at pre-dose and for 48 hours following OC dosing. On Day 10, the morning dose of PF-06650833 and the single OC dose will be administered simultaneously within 5 minnutes. Dosing with PF-06650833 400 mg PO QD will continue until Day 11 (Table 2). Participants will be discharged on Day 12 only after review of safety laboratory by the PI. Figure 1 shows the schematic of Study Design.

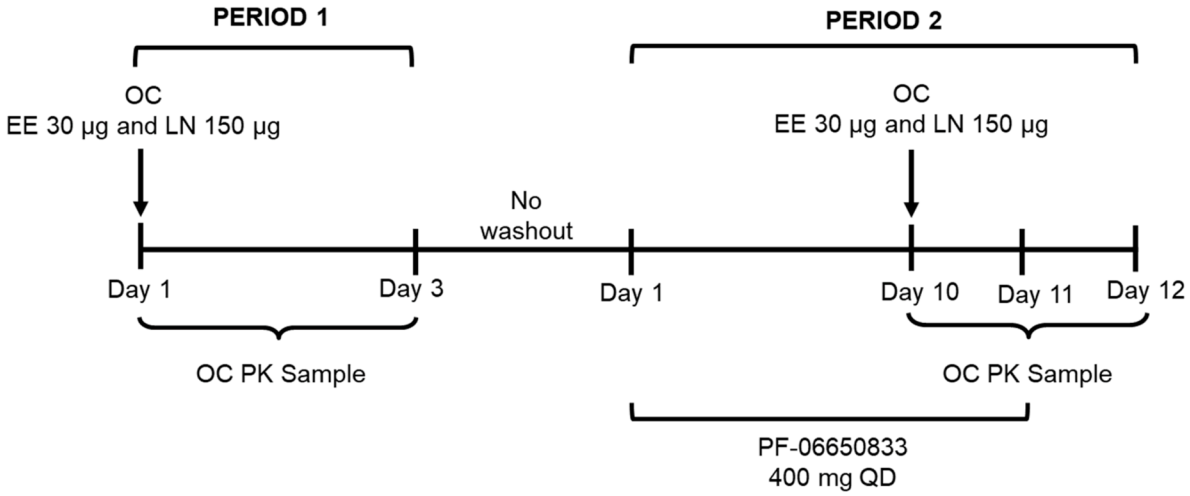
Table 2. Study Design and Treatments

Period 1	Washout	Period 2
Treatment R	None	Treatment T

Treatment R: Single dose of OC in the form of 1 PORTIA® (EE and LN) or equivalent oral tablet, containing EE 30 µg and LN 150 µg.

Treatment T: Single dose of combination OC in the form of 1 PORTIA® (EE and LN) or equivalent oral tablet, containing of EE 30 µg and LN 150 µg on the morning of Day 10 following 9 days of PF-06650833 dosed at 400 mg PO QD. Dosing with PF-06650833 at 400 mg PO QD will continue through until Day 11.

Figure 1. Schematic of Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

C_{max} and AUC_{last} of EE and LN.

3.2. Secondary Endpoints

- Laboratory tests.
- Adverse events.
- Vital signs.

3.3. Tertiary/Exploratory Endpoint(s)

T_{max}, and if data permit CL/F, t½ and AUC_{inf}, of EE and LN.

3.4. Baseline Variables

The following baseline variables will be summarized for each treatment. Details of summary analyses are described in Section 6.

Demographic characteristics:

- Baseline age.
- Gender (female vs. male).

- Race (white, black, Asian, other).
- Baseline body weight.
- Baseline Body Mass.

The baseline data measured at Day 1 are:

- Medical history & demography, medication history.
- Physical Examinations.

For laboratory data, baseline for the "PF+OC" phase is defined as the last measurement collected before administering the first dose of OC at the beginning of Period 2 (ie, P2D10 pre-dose).

For vital signs data, baseline for the "PF-only" phase is defined as the last measurement collected before administering the first dose of PF at the beginning of Period 2 (ie, P2D1 pre-dose), and baseline for the "PF+OC" phase is defined as the last measurement collected before administering the first dose of OC at the beginning of Period 2 (ie, P2D10 pre-dose).

For ECG data, baseline for the "PF+OC" phase is defined as the last measurement collected before administering the first dose of OC at the beginning of Period 1 (ie, P1D1 pre-dose).

3.5. Safety Endpoints

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.*

3.5.1. Adverse Events

An adverse event will be considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time (28 days) will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. Any events occurring following start of treatment or increasing in severity and occur in either of the following three phases: OC, PF-06650833 (Days 1-10 of

Period 2), OC+PF-06650833 (Days 10-12 of Period 2), will be counted as treatment emergent. Events that occur in a non-treatment period (for example, Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

3.5.2. Laboratory Data

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

To determine if there are any clinically significant laboratory abnormalities, the 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 participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Plot of laboratory parameter(s) value and plot of change from baseline may be requested for parameters changing significantly from baseline.

3.5.3. Vital Signs Data

Supine measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

The following vital signs endpoints will be determined:

- The minimum and maximum systolic and diastolic blood pressures and the minimum and maximum pulse rates over all measurements taken post-dose.

- The maximum increase and maximum decrease from baseline over all measurements taken post-dose for systolic and diastolic blood pressures and pulse rates.

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

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

Plot of vital signs parameter(s) values and plot of change from baseline may be requested for parameters changing significantly from baseline.

3.5.4. ECG Results

PR, QT, RR and QTc intervals, QRS and heart rate will be recorded at each assessment time indicated in the Schedule of Activities given in the protocol. QTcF will also be presented and will be derived using Fridericia's heart rate correction formula.

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

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

The maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, PR, RR and QRS, over all measurements taken post-dose, will be determined.

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 will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

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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.

Table 3. Analysis Populations

Population	Description
Enrolled	All participants who sign the informed consent document (ICD). A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Assigned to investigational product	All participants who sign the ICD and meet all eligibility criteria.
PK Concentration Analysis Set	All participants who receive at least 1 dose of investigational product and have at least 1 plasma concentration value reported in at least 1 period.
PK Parameter Analysis Set	All participants who receive at least 1 dose of investigational product and have at least 1 of the PK parameters of primary interest reported in at least 1 period.

Population	Description
Evaluable	All participants enrolled to investigational product and who take at least 1 dose of investigational product.
Safety	All participants enrolled to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or statistical decision rules for PK and safety data.

5.2. General Methods

To assess any effect of PF-06650833 on EE or LN exposures, natural log transformed AUC_{last} and C_{max} will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model and will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

The following assessment should be performed:

- *Effect of PF-06650833 on OC (EE or LN) exposures with OC alone (Period 1 Day 1 PK) as the Reference treatment and co-administration of PF-06650833 and OC (Period 2 Day 10 PK) as the Test treatment.*

Data will be presented – ie, listed and summarized – by treatment/period and overall. Continuous data will be summarized comprising mean, median, standard deviation, minimum and maximum. Categorical and binary data that are summarized will be via percentages. Some measures will be summarized using graphical representations by treatment/period, where appropriate.

The assignment of the reference and test treatment for drug-drug interaction evaluation is shown in Table 4.

Table 4. Assignment of Reference and Test Treatments

Reference Treatment (Observation Time)	Test Treatment (Observation Time)
OC (EE+LN) (PERIOD 1/DAY 1)	PF-06650833 + OC (EE+LN) (PERIOD 2/DAY 10)

Table 5. Calculation and Safety Reporting by Treatment

Treatment Code	Treatments	PK Calculation	Safety reporting
R	OC (EE and LN)	Day 1 PK in Period 1	Period 1
T	OC (EE and LN) + PF-06650833	Day 10 PK in Period 2	Period 2

For summary statistics, median and 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.

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 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.

5.3.2. 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.

5.3.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a 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 treatment with ≥3 evaluable measurements. For statistical analyses (ie, analysis of variance), 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 participantparticipant has a known biased estimate of a 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

6.1. Primary Endpoint(s)

6.1.1. Pharmacokinetic Endpoints

The mixed effects model described in Section 5.2 will be applied to AUC and C_{max}. *The plasma PK parameters in Table 2 will be summarized descriptively by treatment, as applicable, in accordance with Pfizer data standards. AUC_{last} and C_{max} for EE and LN individual participant parameters will be plotted by treatment. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time and treatment. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment using actual and nominal times respectively. Median profiles will be presented on both linear-linear and log-linear scales.*

Blood samples for PK analysis of EE and LN will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters (shown in Table 6) will be calculated for EE and LN (if possible) from the concentration-time data using standard noncompartmental methods:

Table 6. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	EE	LN
C_{max}	ln, R	A, D	A, D
T_{max}	R	D	D
AUC_{last}	ln, R	A, D	A, D
AUC_{inf}*	ln, R	A, D	A, D
CL/F*	R	D	D
PTR	R	D	D
$t_{1/2}$*	R	D	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), NA=not applicable; *=if data permits, C_{max}= Maximum plasma concentration during the dosing interval; T_{max}=Time for C_{max}; AUC_{last}=Area under the plasma concentration-time profile from time

zero to the time of the last quantifiable concentration (C_{last}); AUC_{inf} =Area under the plasma concentration-time profile from time zero extrapolated to infinite time, and dose normalized AUC_{inf}; CL/F=Apparent Clearance; PTR=Peak-to-trough ratio; $t_{1/2}$=Terminal elimination half life.

Table 7. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
C_{max} AUC_{last} AUC_{inf} * CL/F * PTR	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.

* If data permit.

Box and whisker plots for individual participantparticipant parameters (C_{max}, AUC_{last}, and AUC_{inf},) will be presented by treatment (R vs T as described in Table 4) and overlaid with geometric means. There will be a summary table each for OC (EE and LN) presenting all PK parameters.

Supporting data from the estimation of $t_{½}$ will be listed by treatment: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); 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.

Presentations for OC (EE and LN) concentrations will include:

- A listing of all concentrations sorted by participant ID, period and nominal time postdose. 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 and nominal time postdose, 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 plot (on both linear and semi-log scales) against nominal time post dose for reference vs test (treatment R vs T as described in Table 4). Test and reference lines and points will be represented by different colors.

- Mean (±90%CI) concentration time plot (on both linear and semi-log scales) against nominal time post dose for reference vs test (treatment R vs T). Test and reference lines and points will be represented by different colors.

- Individual concentration time plot (on both linear and semi-log scales) against actual time post dose for reference vs test (R vs T Table 4). Test and reference lines and points will be represented by different colors.

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

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

6.2. Safety Summaries and Analyses

All safety analyses will be performed on the safety population and summarized in accordance with Pfizer Data Standards.

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

Safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations, where appropriate. Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome (eg, blood pressure, pulse rate, etc.) will be summarized using N, mean, median, standard deviation, etc. Change from baseline (CFB) in laboratory data, and vital signs will also be summarized. Participant listings will be produced for the safety endpoints accordingly.

6.2.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

6.2.2. Laboratory Data

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

6.2.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline with corresponding standard deviations for supine systolic and diastolic blood pressure and pulse rate for each treatment 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.

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 timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.2.4. Electrocardiograms

ECG

Absolute values in QT, heart rate, QTcB, QTcF, PR and QRS will be summarized by treatment in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Maximum increase from baseline for QTcB, QTcF, heart rate, QT, PR and QRS will be summarized by treatment in accordance with the sponsor reporting standards.

ECG endpoints (QTcB, QTcF, PR and QRS) will also be summarized descriptively by treatment, 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.

7. INTERIM ANALYSES

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/PD modeling, and/or supporting clinical development.

8. REFERENCES

1. 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. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

```
proc mixed data=tab.pk;
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /participant=participant;
        lsmeans trt /cl alpha=0.1;
        estimate 'Test vs Reference' trt -1  1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;


/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
    (R (OC) = Reference; T (PF-06650833+OC) = Test)  */;
```

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	
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 clinical study report.

Appendix 3. List of Abbreviations

Abbreviation	Term
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 zero to the time of the last quantifiable concentration (C_{last})
BLQ	below the limit of quantification
BP	blood pressure
C_{last}	last quantifiable concentration
C_{max}	maximum plasma concentration during the dosing interval
CFB	change from baseline
CI	confidence interval
CL/F	apparent clearance
CRU	clinical research unit
CV	coefficient of variation
ECG	electrocardiogram
EE	ethinyl estradiol
ICD	informed consent document
ID	identification
k_{el}	terminal phase rate constant
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LLQ	lower limit of quantitation
LN	levonorgestrel
MR	modified release
NC	Not calculated
ND	not done
NS	no sample
OC	oral contraceptive
PD	pharmacodymic
PI	principal investigator
PK	pharmacokinetic
PO	by mouth
PTR	peak-to-trough ratio
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
r^2	the goodness-of-fit statistic from the regression
SAP	statistical analysis plan
SAE	serious adverse event
T_{max}	Time for C_{max}

Abbreviation	Term
$t_{½}$	terminal elimination half-life
TEAE	treatment emergent adverse event