Protocol C3991047

A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE STUDY TO ESTIMATE THE EFFECT OF PF-07081532 ADMINISTRATION ON THE SINGLE-DOSE PHARMACOKINETICS OF DABIGATRAN AND ROSUVASTATIN IN OVERWEIGHT OR OBESE ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: **2**

Date: 04 Jul 2023

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

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 24 Mar 2023	Original 31 Jan 2023	N/A	N/A
2 04 Jul 2023	N/A	In order to be consistent with C3991004 IRC Charter (01-May-2023) inclusion of LFTs outputs.	Addition of Sections 3.2.1.2 and 6.2.1.2.1 describing additional outputs related to LFTs to be reported and the expected outputs.
		Dosing of PF-07081532 was capped at 240mg QD.	Addition of text to Section 2.1 to explain the change of design from the protocol.
		Changes to vital signs thresholds to include a maximum threshold for SBP and DBP	Changes to Appendix 2 – Categories for Vital Signs
		These definitions of baseline were not being used in any analyses	Removal of the definitions of baseline for C-SSRS and PHQ-9
		Analyses are not needed as sufficient participants got to 240mg QD	Removed sensitivity analysis for Section 6.1.1

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991047.

2.1. Modifications to the Analysis Plan Described in the Protocol

Due to the dosing of PF-07081532 being capped at 240mg QD, the titration of PF-07081532 stopped at the end of Period 6 and the study was shortened by 6 days. Therefore, the study design presented in Section 2.3 is accurate according to study protocol but not the most up to date study design for C3991047, in terms of dose and execution day.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint
	Primary:	**Primary:**
PK Section 6.1	• *To estimate the effect of PF-07081532 administration on the single-dose PK of total dabigatran in otherwise healthy overweight or obese participants.*	• *Dabigatran (total) PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4, and 7.*
PK Section 6.1	• *To estimate the effect of MD PF-07081532 on the single-dose PK of rosuvastatin in otherwise healthy overweight or obese participants.*	• *Rosuvastatin PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5, and 8.*
	Secondary:	**Secondary:**
Safety Section 6.2	• *To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with DE in otherwise healthy overweight or obese participants.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters.* • *Assessment of mental health as determined by C-SSRS and PHQ-9.*
Safety Section 6.2	• *To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with rosuvastatin in otherwise healthy overweight or obese participants*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters.* • *Assessment of mental health as determined by C-SSRS and PHQ-9.*
PK Section 6.2.2.1	• *To evaluate the effects of PF-07081532 on additional PK parameters for total dabigatran.*	• *Additional plasma PK parameters for total dabigatran: C_{max} and T_{max}; and CL/F, V_z/F, $t_{½}$ as data permit, in Periods 1, 4, and 7.*
PK Section 6.2.2.1	• *To evaluate the effects of PF-07081532 on additional PK parameters for rosuvastatin.*	• *Additional plasma PK parameters for rosuvastatin: C_{max} and T_{max}; and CL/F , V_z/F, $t_{½}$ as data permit, in Periods 2, 5, and 8.*
PK Section 6.2.2.2	• *To evaluate the MD pharmacokinetics of PF-07081532 in healthy overweight or obese participants.*	• *PF-07081532 plasma pharmacokinetic parameters: AUC_{24}, C_{max}, T_{max}.*
	Tertiary:	**Tertiary:**
CCI [redacted]		

**Should it be deemed that too few AUC_{inf} estimates (e.g. less than 16 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin and dabigatran objectives separately.*

There are no estimands for this study.

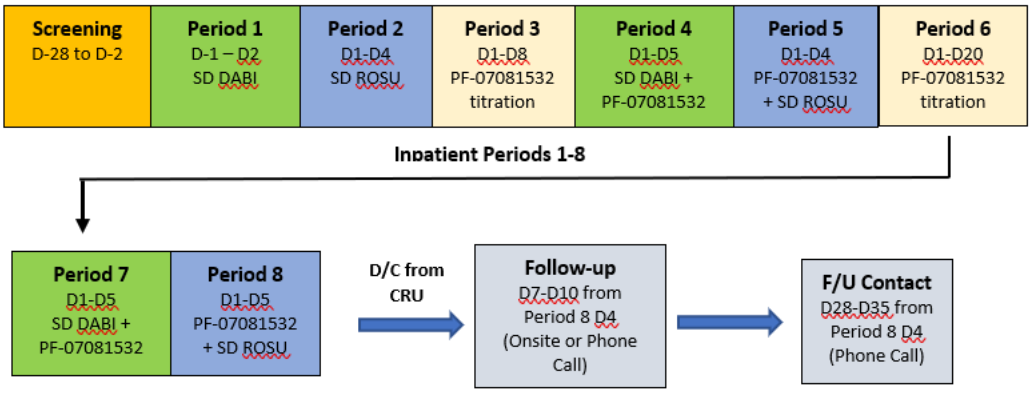
2.3. Study Design

This study *is a Phase 1, open-label, fixed-sequence, 8-period study to evaluate the effect of PF-07081532 administration on the SD pharmacokinetics of* total *dabigatran and rosuvastatin in otherwise healthy overweight or obese adult participants. The 8 periods will be conducted sequentially without any washout days between periods.*

All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. Screening will occur within 28 days of the first dose of study intervention on Day 1 of Period 1. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

Approximately 24 participants will be enrolled such that approximately 16 evaluable participants complete the study.

Figure 1. Study Design



The total duration of participation from the Screening Visit to the F/U outpatient telephone contact will be approximately 115 days or 16.5 weeks, approximately 8 weeks of which will be conducted on an inpatient basis.

The 54-day inpatient portion of the study will be conducted as follows:

Period 1: 3 days, includes CRU admission on Day -1 (DE 150 mg single dose);

Period 2: 4 days (rosuvastatin 10 mg single dose);

Period 3: 8 days (PF-07081532 titrated to 40 mg QD);

Period 4: 5 days (DE 150 mg single dose + PF-07081532 80 mg QD);

Period 5: 4 days (rosuvastatin 10 mg single dose + PF-07081532 80 mg QD);

Period 6: 20 days (PF-07081532 titrated to 240 *mg QD);*

Period 7: 5 days (DE 150 mg single dose + PF-07081532 240 *mg QD);*

Period 8: 5 days, includes discharge day from CRU (rosuvastatin 10 mg single dose + PF-07081532 240 *mg QD).*

The onsite F/U visit/telephone F/U contact will occur 7-10 days from the last dose of study intervention (Period 8, Day 4) and an outpatient telephone F/U contact will occur 28-35 days from the last dose of study intervention (Period 8, Day 4).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Blood samples for PK analysis of total dabigatran, rosuvastatin, and PF-07081532 will be collected according to the Schedule of Activities given in the protocol.

PK parameters and CCI will be calculated (if possible) from the concentration-time data using standard noncompartmental methods.

3.1. Primary Endpoint(s)

- *Dabigatran (total)* plasma *PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4, and 7.*
- *Rosuvastatin* plasma *PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5, and 8*

**Should it be deemed that too few AUC_{inf} estimates (e.g. less than 16 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin and* total *dabigatran objectives separately.*

AUC_{last} will be calculated and reported regardless of whether AUC_{inf} is the primary endpoint for CSR reporting or not. The plasma PK parameters in Table 2 will be determined:

Table 2. Summary of primary total dabigatran and rosuvastatin plasma PK parameters to be calculated.

Parameter	Analysis Scale	Dabigatran Etexilate 150mg (Periods 1, 4 and 7)	Rosuvastatin 10mg (Periods 2, 5 and 8)
AUC_{inf}*	ln	A, D	A, D
AUC_{last}	ln	A, D	A, D

*=if data permits. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 7 in Section 6.1.1 ; ln=natural-log transformed.

3.2. Secondary Endpoint(s)

3.2.1. Safety Endpoints

- *Assessment of* treatment-emergent adverse events (*TEAEs*), *clinical laboratory abnormalities, vital signs, body weight, and ECG parameters* during the entire study, by period.

Any events occurring following start of study intervention (i.e. treatment) will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the most recent treatment taken.

A 3-tier approach for summarizing adverse events (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 (except data from screening visit),
- vital signs data,
- body weight
- ECG results.

For laboratory, vital signs, ECG data, laboratory data and body weight, baseline is defined as the last pre-dose measurement in Period 1.

3.2.1.1. Additional Safety Endpoints of Interest

- Change from baseline in body weight at all post-dose time points as outlined in the SoA
- Percent change from baseline in body weight at all post-dose time points as outlined in the SoA
- Change from baseline in fasting plasma glucose at all post-dose time points as outlined in the SoA
- Change from baseline in HbA1c at all post-dose time points as outlined in the SoA

For these additional endpoints, baseline is defined as the last pre-dose measurement in Period 1 (i.e. Day -1).

3.2.1.2. Laboratory Parameters of Interest – Liver Function Tests

Normalized values for liver function tests as described in Table 3 will be derived and a flag for each level of abnormality (ie "Flag Level" or "Alert Level") will be included in the derived dataset. If abnormalities persist across periods for the same participant these should be reported across the multiple periods.

Table 3. Liver Function Tests of Interest

Parameter	Flag Level	Alert Level	Conventional Units
Alanine aminotransferase	> ULN	-	U/L
	> 2x ULN	-	U/L
	> 3x ULN	-	U/L
	> 5x ULN	> 8x ULN	U/L
	> 5x ULN	> 10x ULN	U/L
	> 5x ULN	> 20x ULN	U/L
Aspartate aminotransferase	> ULN	-	U/L
	> 2x ULN	-	U/L
	> 3x ULN	-	U/L
	> 5x ULN	> 8x ULN	U/L
	> 5x ULN	> 10x ULN	U/L
	> 5x ULN	> 20x ULN	U/L
Alkaline Phosphatase	> 2x ULN	-	U/L
	> 3x ULN	-	U/L
	> 5x ULN	-	U/L
Total Bilirubin	> 2x ULN	> 3x ULN	mg/dL
Direct and Indirect Bilirubin	> ULN	-	mg/dL

ULN – Upper Limit of Normal as determined by the central laboratory

3.2.2. Assessment of Mental Health

- *Assessment of mental health as determined by C-SSRS and PHQ-9* during the entire study.

3.2.2.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behaviour.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes as given in Appendix 4.

3.2.2.2. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms. The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the schedule of activities (*SoA*).

The PHQ-9 total score will be derived for each time point separately by summing the responses to the 9 questions.

3.2.3. Additional plasma PK Parameters for total Dabigatran and Rosuvastatin

- *Additional plasma* pharmacokinetic (*PK)* parameters *for total dabigatran (Periods 1, 4 and 7: C_{max}, T_{max}, and CL/F, V_z/F, $t_{½}$, as data permit*
- *Additional plasma* pharmacokinetic *(PK) parameters for rosuvastatin (Periods 2, 5 and 8): C_{max}, T_{max}, and CL/F, V_z/F, $t_{½}$, as data permit*

The additional plasma PK parameters for total dabigatran and rosuvastatin in Table 4 will be determined:

Table 4. Summary of additional total dabigatran and rosuvastatin plasma PK Parameters to be calculated

Parameter	Analysis Scale	Dabigatran Etexilate 150mg (Periods 1, 4 and 7)	Rosuvastatin 10mg (Periods 2, 5 and 8)
C_{max}	Ln	A, D	A, D
T_{max}	R	D	D
$t_{½}$*	R	D	D
CL/F*	Ln	D	D
V_z/F*	Ln	D	D

*=if data permits. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 8 in Section 6.2.2.1; ln=natural-log transformed; R=raw (untransformed).

3.2.4. Plasma PK Parameters for PF-07081532

- *PF-07081532 plasma pharmacokinetic parameters* at Study Days 19 and 48*: AUC_{24}, C_{max}, T_{max}.*

The plasma PK parameters for PF-07081532 in Table 5 will be determined:

Table 5. Summary of PF-07081532 plasma PK Parameters to be calculated

Parameter	Analysis Scale	PF-07081532 80mg QD (Day 19)	PF-07081532 240mg QD (Day 48)
AUC_{24}	Ln	D	D
C_{max}	Ln	D	D
T_{max}	R	D	D

Abbreviations: D=displayed with descriptive statistics as outlined in Table 9 in Section 6.2.2.2; ln=natural-log transformed; R=raw (untransformed).

3.3. Other Endpoint(s)

CCI

[redacted]

3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

See Section 3.2 for details.

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.

Participant Analysis Set	***Description***
Enrolled	*"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 and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. 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 assigned to study intervention and who take at least 1 dose of study intervention.
Safety analysis set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.*
PK Concentration Set	*The PK concentration population is defined as all participants who receive at least 1 dose of rosuvastatin, dabigatran* etexilate*, and/or PF-07081532 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 receive at least 1 dose of rosuvastatin, dabigatran etexilate, and/or PF-07081532 and have at least 1 of the PK parameters of interest calculated.* *Should vomiting occur after co-administration of rosuvastatin or dabigatran* etexilate *with PF-07081532, the resulting PK parameters from that participant from the corresponding period may be excluded, where further details* are provided in Section 5.3.

5. GENERAL METHODOLOGY AND CONVENTIONS

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

Unless otherwise stated, all summaries and plots will be presented by treatment group (equivalent to 'by Period'). The following treatment labels (or similar) will be used, which represent Periods 1 to 8 as:

Period	Treatment Label
1	Dabigatran etexilate 150 mg (Period 1)
2	Rosuvastatin 10 mg (Period 2)
3	PF-07081532 titration up to 40 mg QD (Period 3)
4	PF-07081532 80 mg QD + dabigatran etexilate 150 mg (Period 4)
5	PF-07081532 80 mg QD + rosuvastatin 10 mg (Period 5)
6	PF-07081532 titration up to 240 mg QD (Period 6)
7	PF-07081532 240 mg QD + dabigatran etexilate 150 mg (Period 7)
8	PF-07081532 240 mg QD + rosuvastatin 10 mg (Period 8)

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. Mixed effects model

A mixed effects model with treatment as a fixed effect and participant as a random effect will be used. *Estimates of the adjusted* (least squares) *mean differences (Test-reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.*

The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and the Kenward-Roger degrees of freedom algorithm.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers (where studentized [conditional] residuals are greater than 3 or less than -3) then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study if applicable.

Example code is shown 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 exploratory safety data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLOQ).

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 "<LLOQ", where LLOQ will be replaced with the value for the LLOQ.

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/statistician.

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 effects 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, e.g., within 2 times the median T_{max} after the last dose for the respective treatment[1]), 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

For all presentations, study day will refer to the day within a particular treatment period, unless otherwise specified.

6.1. Primary Endpoint(s)

6.1.1. AUC_{inf} and AUC_{last} for Total Dabigatran and Rosuvastatin

The PK data for rosuvastatin, total dabigatran, and PF-07081532 will be analyzed and reported separately.

AUC_{inf} and AUC_{last} for total dabigatran and rosuvastatin alone and co-administered with PF-07081532 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Natural log_e transformed AUC_{inf} (as data permit), and *AUC_{last} of* total *dabigatran administered without PF-07081532 on Period 1 or coadministered with PF-07081532 in Period 4 and on Period 7 will be analyzed using a mixed effect model* as described in Section 5.2.3.

The 2 test treatments will be 'dabigatran and PF-07081532 80 mg QD' (Period 4) and 'dabigatran and PF-07081532 240 mg QD' *(Period 7), which will be reported separately in comparison to the reference treatment of 'dabigatran without PF-07081532' (Period 1).*

Natural log_e transformed AUC_{inf} (as data permit), and *AUC_{last} of rosuvastatin administered alone in Period 2 or coadministered with PF-07081532 on Period 5 and Period 8 will be analyzed and reported separately using the same mixed effect model as described above for* total *dabigatran. The 2 test treatments will be 'rosuvastatin and PF-07081532 80 mg QD' (Period 5) and 'rosuvastatin and PF-07081532* 240 mg QD' *(Period 8), which will be*

reported separately in comparison to the reference treatment of 'rosuvastatin without PF-07081532' (Period 2).

In the event that participants do not successfully titrate to the target PF-07081532 doses by the end of Periods 3 and/or 6, the related PK parameters for total dabigatran and rosuvastatin in the subsequent periods would not be included in the above models (but may be included in sensitivity analyses described below). Note this implies that evaluable PK parameters for the same participants from at least Period 1 (for total dabigatran) and 2 (for rosuvastatin) would be included in the models.

AUC_{inf} and AUC_{last} will be listed, summarized for each treatment (total dabigatran and rosuvastatin will be reported in separate tables) as specified in the table below:

Table 7. Summary statistics to be produced for plasma PK Parameters of total dabigatran and rosuvastatin

Parameter	Summary Statistics
AUC_{last} & AUC_{inf}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

Supporting data from the estimation of AUC_{inf} will be listed by treatment: 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.

As a sensitivity analysis an additional physiologically-based PK or other related model may be explored if fewer than 16 participants have PK parameters as above to further characterize the relationship between PK of PF-07081532 and PK of total dabigatran and/or rosuvastatin, which would be reported outside of the CSR.

The following plots will be presented:

- Box and whisker plots for individual PK parameters (AUC_{inf} and AUC_{last}) will be presented by treatment and overlaid with geometric means. These will be produced for total dabigatran and rosuvastatin PK parameters separately.

The following will additionally be presented for the plasma concentration data of total dabigatran and rosuvastatin (reported in separate tables) 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 treatment (i.e. total dabigatran and rosuvastatin dosed alone or co-administered, as applicable) separately. 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 each nominal time post-dose (produced separately for each treatment), 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 treatment. Two plots will be presented for each scale: one for the three treatments with total dabigatran and another for the three treatments with rosuvastatin.
- individual concentration time plots by treatment (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each treatment, with a line for each participant per scale). Plots for total dabigatran and rosuvastatin will be produced separately.
- individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. Two plots for each participant and scale will be presented: one for the three treatments with total dabigatran and one for the three treatments with rosuvastatin.

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.

6.2. Secondary Endpoint(s)

6.2.1. Safety Endpoints

6.2.1.1. Adverse Events

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

Incidence and severity of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarize the total number of adverse events by preferred term, which will be reported by treatment and overall in accordance with sponsor reporting standards using the safety analysis set defined in Section 4.

The AEs will be presented sorted in descending frequency based on the overall number of AEs (by preferred term or system order class as appropriate) across treatments.

6.2.1.2. Laboratory Data

Laboratory data will be listed and summarized by treatment and overall, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Change from baseline (as defined in Section 3.2.1) summaries will be presented. In summary and listing tables, laboratory abnormalities occurring pre-dose on Day 1 during Periods 2-8, will be attributed to the treatment from the previous Period (e.g., an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.1.2.1. Additional Summaries for Liver Function Tests

Using the safety population defined in Section 4, the number of participants with values meeting the flag or alert boundaries as defined in Table 3 for each of the parameters will be summarized (as specified in Section 5.2.2), by period/treatment and overall. All planned and unplanned post baseline time points will be counted in these categorical summaries.

Figure:

For ALT, AST, ALP, Total Bilirubin and Direct Bilirubin, individual normalized values (i.e. raw value divided by the upper limit of normal) over time (i.e. spaghetti plot) will be reported. Reference lines for flag and alert levels crossing Y-axis will be displayed. Screening and unplanned collections before Day 1 will not be included in individual plots. All other unplanned visits will be included. If two or more values are collected on the same day, all collections will be included in the plot. A reference median line will also be included in the plots. Screening, unplanned and early termination collections will not be included in the median calculation. For any value over 3xULN the subject ID will be displayed in the plot.

6.2.1.3. Vital Signs

Absolute values and changes from baseline (as defined in Section 3.2.1) in supine systolic and diastolic blood pressure and pulse rate will be listed, and summarized by treatment and time point, according to sponsor reporting standards using the safety population defined in Section 4.

Mean absolute values and mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time point i.e., analysis visit. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum and minimum absolute values and changes from baseline (as defined in Section 3.2.1) for supine vital signs 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 time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed. Values meeting the categorical criteria occurring pre-dose on Day 1 during Periods 2-8, will be attributed to the treatment from the previous Period (e.g., an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.1.4. Electrocardiogram (ECG)

Absolute values and changes from baseline (as defined in Section 3.2.1) in QT interval, heart rate, QTcF interval, PR interval and QRS interval will be listed, and summarized by treatment and time point using sponsor reporting standards using the safety population defined in Section 4. Tables will be paged by parameter.

Mean changes from baseline for QT interval, heart rate and QTcF interval will be plotted against time point i.e., analysis visit. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum absolute values and changes from baseline for QTcF, PR and QRS 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. Values meeting the categorical criteria occurring pre-dose on Day 1 during Periods 2-8, will be attributed to the

treatment from the previous Period (e.g., an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.1.5. Additional Safety Endpoints of Interest

Absolute values and changes from baseline for body weight (both absolute and percent change, separately), fasting glucose and HbA1c will summarized by treatment and time point as outlined in Section 5.2.1 for participants in the safety population (as defined in Section 4).

6.2.1.6. C-SSRS

Baseline and post-baseline C-SSRS data (mapped to C-CASA scores as described in Section 3.2.2.1) using the safety population defined in Section 4 will be summarized categorically by treatment and time point as outlined in Section 5.2.2.

6.2.1.7. PHQ-9

Baseline and post-baseline PHQ-9 data (responses to each of the 9 items) using the safety population defined in Section 4, will be summarized categorically for each question separately by treatment and time point as outlined in Section 5.2.2.

The PHQ-9 total score as defined in Section 3.2.2.2 will additionally be summarized descriptively by treatment group and time point as outlined in Section 5.2.1.

6.2.1.8. Mental Health Risk Assessment

The number of participants who met the criteria for referral to a mental health professional will be listed and summarized by treatment group and time point as outlined in Section 5.2.2.

6.2.2. Additional Plasma PK Parameters

6.2.2.1. Additional Plasma PK Parameters for Total Dabigatran and Rosuvastatin

C_{max}, T_{max}, CL/F, V_z/F, $t_{½}$ for total dabigatran and rosuvastatin alone and co-administered with PF-07081532 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

C_{max}, T_{max}, CL/F, V_z/F, $t_{½}$ will be summarized for each treatment (total dabigatran and rosuvastatin will be reported in separate tables) as specified in the table below:

Table 8. Summary statistics to be produced for additional plasma PK Parameters for total dabigatran and rosuvastatin

Parameter	Summary Statistics
C_{max}, CL/F, V_z/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{½}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Natural log_e transformed C_{max} of total *dabigatran administered without PF-07081532 on Period 1 or coadministered with PF-07081532 in Period 4 and on Period 7 will be analyzed using a mixed effect model* as described in Section 5.2.3.

The 2 test treatments will be 'dabigatran and PF-07081532 80 mg QD' (Period 4) and 'dabigatran and PF-07081532 240 mg QD' *(Period 7), which will be reported separately in comparison to the reference treatment of 'dabigatran without PF-07081532' (Period 1).*

Natural log_e transformed C_{max} of rosuvastatin administered alone in Period 2 or coadministered with PF-07081532 on Period 5 and Period 8 will be analyzed and reported separately using the same mixed effect model as described above for total *dabigatran. The 2 test treatments will be 'rosuvastatin and PF-07081532 80 mg QD' (Period 5) and 'rosuvastatin and PF-07081532* 240 mg QD' *(Period 8), which will be reported separately in comparison to the reference treatment of 'rosuvastatin without PF-07081532' (Period 2).*

The following plots will be presented:

- Box and whisker plots for individual C_{max} will be presented by treatment and overlaid with geometric means. These will be produced for total dabigatran and rosuvastatin C_{max} separately.

6.2.2.2. Plasma PK Parameters for PF-07081532

Plasma PK parameters for PF-07081532 as described in Section 3.2.4 will be listed and summarized descriptively for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

AUC_{24}, C_{max}, T_{max} will be summarized for each treatment period of PF-07081532 as required in the table below:

Table 9. Summary statistics to be produced for plasma PK Parameters for PF-07081532

Parameter	Summary Statistics
AUC_{24}, C_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.

The following plots will be presented:

- Box and whisker plots for individual PK parameters of PF-07081532 (AUC_{24} and C_{max}) will be presented by treatment and overlaid with geometric means.

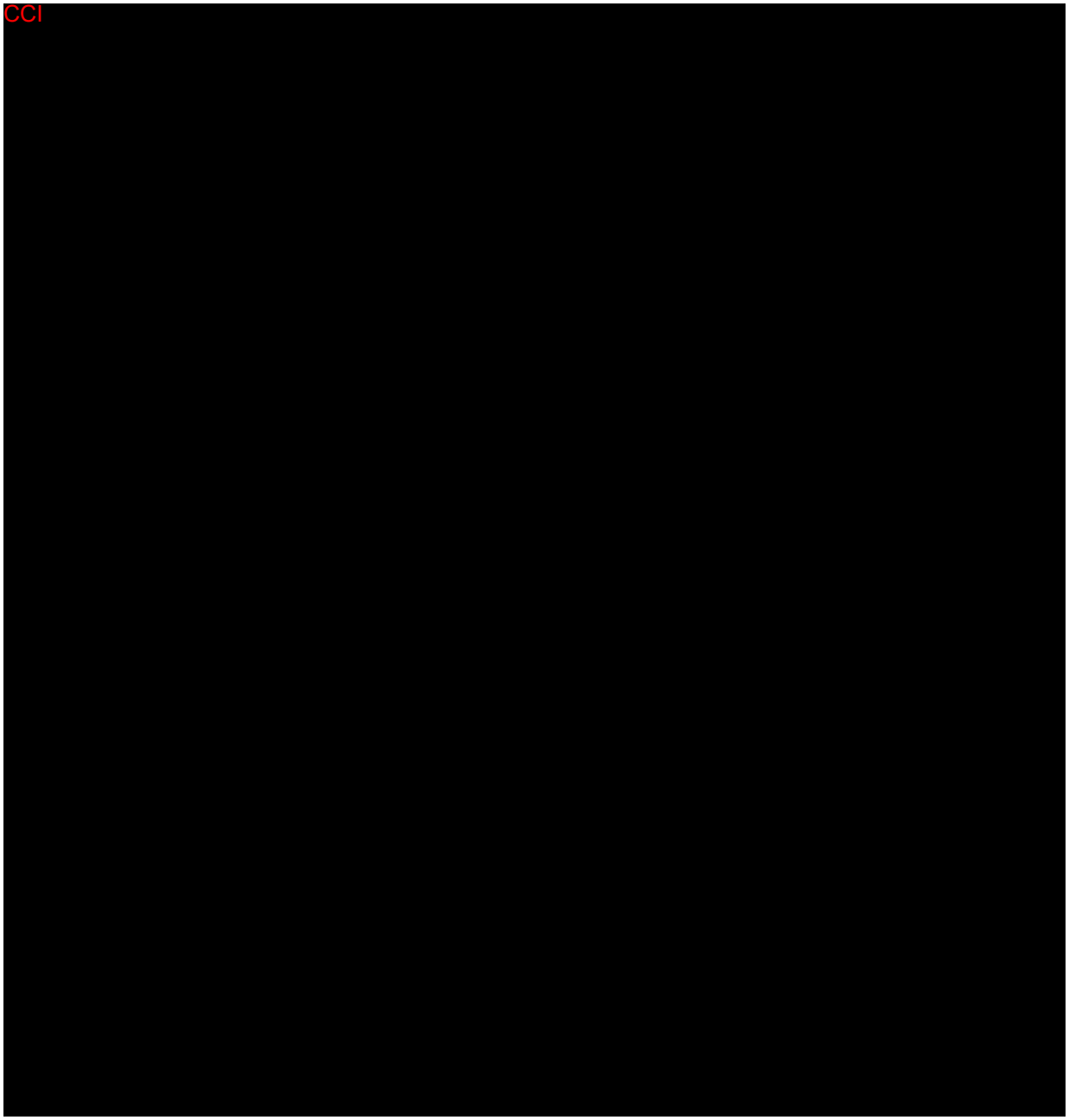
The following summaries will additionally be presented for the plasma concentration data of PF-07081532 using the PK Concentration Set (as defined in Section 4):

- a listing of all concentrations sorted by participant ID and nominal time post-dose for each PF-07081532 treatment period separately. 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 each nominal time post-dose (produced separately for each treatment period), 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 treatment period. One plot for each scale will be presented which will include both PF-07081532 treatment periods in the same plot.
- individual concentration time plots by treatment period (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each treatment period, with a line for each participant per scale).
- individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. One plot for each participant and scale will be presented, which will include both PF-07081532 treatment periods in the same plot.

For summary statistics and median 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. Median profiles will be presented on both linear-linear and log-linear scales.

6.3. Other Endpoint(s)

CCI



6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics data (age, biological sex, race, ethnicity, body weight, body mass index and height) will be summarized across all participants in the safety population (as defined in Section 4) as described in Section 5.2.1 or Section 5.2.2 (as appropriate).

6.5.2. Study Conduct and Participant Disposition

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

6.5.3. Study Treatment Exposure

Not applicable.

6.5.4. Concomitant Medications and Nondrug Treatments

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

6.6. Safety Summaries and Analyses

See Section 6.2.

7. INTERIM ANALYSES

7.1. Introduction

No 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 and PK assessment, facilitating PK/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1) Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations. *Draft Guidance from the FDA*. March 2014.

APPENDICES

Appendix 1. PK Analyses – Example of SAS Code for mixed effects model

An example of the PROC MIXED code:

```
proc mixed data=tab.pk;
        class trt subject;
        model &var = trt / ddfm=KR;
        random subject /subject=subject;
        lsmeans trt/ diff cl alpha=0.1;
run;
```

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

Categories for QTcF

Degree of Prolongation	**Mild (ms)**	**Moderate (ms)**	**Severe (ms)**
Absolute value of QTcF	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF	>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	max. >200
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	max. >100
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
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{inf}	Area Under the Concentration-Time Curve from time zero extrapolated to infinity
AUC_{last}	Area Under the Concentration-Time Curve from time zero to the last measurable concentration
AUC_{24}	Area Under the Concentration-Time Curve from time zero to time 24 hours
BLQ	Below the Limit of Quantitation
bpm	Beats per minute
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
CCI [redacted]	[redacted]
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DE	Dabigatran etexilate
dL	Deciliter
ECG	Electrocardiogram
F/U	Follow Up
HbA1c	Haemoglobin A1c
CCI [redacted]	[redacted]
ID	Identification
CCI [redacted]	[redacted]
IRC	Internal Review Committee
LFT	Liver Function Test
LLOQ	Lower Limit of Quantitation
ln	Natural log
MD	Multiple dose
mg	milligram
mmHg	Millimetres of Mercury
ms	Millisecond
N	Sample Size

Abbreviation	Term
N/A	Not Applicable
NC	Not Calculated
ND	Not Done
NS	No Sample
CCI	[redacted]
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PHQ-9	Patient Healthy Questionnaire 9
QD	Once a Day
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Single Dose
SoA	Schedule of Activities
TEAEs	Treatment Emergent Adverse Events
T_{max}	Time to maximum observed concentration
$t_{½}$	Half life
U/L	Units per Litre
ULN	Upper Limit of Normal
V_z/F	Apparent volume of distribution

Appendix 4. C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior Events and Codes

SSRS Mapped to C-CASA (Suicidality Events and Codes)

Event Code	C-CASA Event	C-SSRS Response
Suicidal Ideation		
1	Passive	"Yes" on "Wish to be dead"
2	Active: Nonspecific (no method, intent, or plan)	"Yes" on "Non-Specific Active Suicidal Thoughts"
3	Active: Method, but no intent or plan	"Yes" on "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act"
4	Active: Method and intent, but no plan	"Yes" on "Active Suicidal Ideation with Some Intent to Act, without Specific Plan"
5	Active: Method, intent, and plan*	"Yes" on "Active Suicidal Ideation with Specific Plan and Intent"
Suicidal Behavior		
1	Completed suicide	"Yes" on "Completed Suicide"
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Interrupted attempt	"Yes" on "Interrupted attempt"
4	Aborted attempt	"Yes" on "Aborted attempt"
5	Preparatory actions toward imminent suicidal behaviors	"Yes" on "Preparatory Acts or Behavior"
Self-injurious behavior, no suicidal intent		
	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

*According to C-SSRS, the definition of *plan* includes intent (i.e., intent to complete the suicide is implicit with the concept of plan). Thus, there is no need for the category *method and plan, but no intent.*