Protocol C4671001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO CONTROLLED, SINGLE- AND MULTIPLE-DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07321332 IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: **2.0**

Date: 25 Aug 2021

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 19 Feb 2021	Original 28 Jan 2021	N/A	N/A
2.0 25 Aug 2021	Amendment 2 02 Jun 2021 Amendment 3 24 Jun 2021 PACL 14 Jul 2021	PART-4 was added to evaluate metabolism and excretion and other updates to be in-line with protocol amendment PART-5 was added to evaluate safety and tolerability of PF-07321332 at supratherapeutic exposure and other updates to be in-line with protocol amendment	• Included PART-4 and PART-5 and removed the specification of PART-3 as optional in the description from the protocol (Section 2). • Updated Figure 1 to include PART-4 and PART-5. • Defined endpoints and baseline variables for PART-4 and PART-5 (Section 3). • Defined an additional analysis set, the Excretion Analysis Set, for PART-4 (Section 4). • Specified analysis methods for PART-4 and PART-5 (Section 6). • Updated minor changes following table review.

2. INTRODUCTION

The current study is the first clinical administration with PF-07321332. It is a 5-part study combining ***PART-1: SAD, PART-2: MAD, PART-3: relative bioavailability/food effect, PART-4: metabolism and excretion*** *and* ***PART-5 supratherapeutic exposure (SE)****. PART-1 and 2 are randomized, double-blind, sponsor-open, placebo-controlled trial to evaluate safety, tolerability and PK of single and multiple escalating oral doses of PF-07321332 in*

*healthy adult participants and **PART-3** is a randomized open label study to evaluate relative bioavailability and food effect of an oral tablet formulation. **PART-2** of the study may also evaluate the safety tolerability and PK in Japanese participants. **PART-4** is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. **PART-5** is a double-blind, sponsor-open, randomized, cross-over study to evaluate safety and tolerability at supratherapeutic exposures.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4671001. 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

There are no estimands for this study.

PART-1: SAD

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• *To assess the safety and tolerability following a single dose of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).*	N/A	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital sign measurements and 12-lead ECG parameters.*
Secondary:	**Secondary:**	**Secondary:**

• *To assess the plasma PK profile of PF-07321332 following single ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir)*	N/A	• *Plasma PK parameters of PF-07321332:*
		  • *C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).*
		  • *If data permits, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.*

Tertiary/Exploratory:	**Tertiary/ Exploratory:**	**Tertiary/Exploratory:**
• *To explore metabolites in plasma, urine, and feces, if data permits.*	N/A	• *Qualitative characterization of metabolites of PF−07321332 in pooled plasma, urine, and feces as data permits.*
• *Quantitative excretion of drug-related material using ^{19}F-NMR spectroscopy, if data permits.*	N/A	• *Total excretion of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered, if data permits.*
• *To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension, if evaluated (Optional)*	N/A	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.*
• *To evaluate the effect of food (high fat meal) on the exposure of PF-07321332 following a single oral dose of PF 07321332 tablet formulation, if evaluated (Optional)*	N/A	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.*

PART-2: MAD (including optional Japanese cohort)

Objectives	Estimand	Endpoints
Primary:	**Primary:**	**Primary:**
• *To assess the safety and tolerability following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).*	N/A	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital sign measurements and 12-lead ECG parameters.*
Secondary:	**Secondary:**	**Secondary:**
• *To assess the plasma PK profile of PF-07321332 on Days 1, 5 and 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).*	N/A	• *Plasma PK parameters of PF-07321332:* • *C_{max}, T_{max}, AUC_{tau} (where tau=8 hours for TID dosing or 12 hours for BID dosing), C_{min}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F.* • *If data permit, $t_{½}$.*
• *To assess the urinary PK profile of PF-07321332 on Day 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).*	N/A	• *PF-07321332 urinary PK parameters:* • *Ae_{tau} and Ae_{tau}%, CL_r*
Tertiary/Exploratory:	**Tertiary/ Exploratory:**	**Tertiary/Exploratory:**
• *To explore metabolites in plasma if data permits.*	N/A	• *Qualitative characterization of metabolites of PF-07321332 in pooled plasma if data permits.*
• *To explore PK by microsampling technique(s), if evaluated (Optional).*	N/A	• *Concentration of PF-07321332, if evaluated.*

PART-3: Relative Bioavailability/Food Effect Cohort

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• *To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension.*	N/A	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.*
Secondary:	**Secondary:**	**Secondary:**
• *To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07321332 following a single oral dose of PF-07321332 tablet formulation.*	N/A	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.*
• *To determine the pharmacokinetics of PF-07321332 following oral administration of tablet and suspension of PF-07321332.*	N/A	• *Plasma PK parameters of PF-07321332: T_{max}, C_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn), if data permits AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL/F, V_z/F.*
• *To determine the safety and tolerability of PF-07321332 following oral administration of tablet and suspension of PF-07321332.*	N/A	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital sign measurements and 12-lead ECG parameters.*
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PART-4: Metabolism and Excretion

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• *To determine the extent of excretion of drug related material in urine and feces after a single oral administration of PF-07321332 with PK boosting agent ritonavir.*	N/A	• *Total recovery of drug related material in urine and feces separately, and both routes combined, expressed as a percent of total oral dose administered.*
Secondary:	**Secondary:**	**Secondary:**
• *To determine the pharmacokinetics of PF-07321332 following oral administration of PF-07321332 with PK boosting agent ritonavir.*	N/A	• *Plasma PK parameters of PF-07321332: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.*
• *To determine the safety and tolerability of PF-07321332 after a single oral administration of PF-07321332 with PK boosting agent ritonavir.*	N/A	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital signs measurements and 12-lead ECG parameters.*
Tertiary/Exploratory:	**Tertiary/ Exploratory:**	**Tertiary/Exploratory:**
• *To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of PF-07321332 with PK boosting agent ritonavir, if possible.*	N/A	• *Metabolic profiling/identification and determination of relative abundance of PF-07321332 and the metabolites of PF-07321332 in plasma, urine, and feces, if possible.*

PART-5: Supratherapeutic Exposure (NH CRU only)

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• *To assess the safety and tolerability of a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritanovir) administrered as split dosing.*	N/A	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to AEs.* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital sign measurements and 12-lead ECG parameters*
Secondary:	**Secondary:**	**Secondary:**

• *To assess the plasma PK of PF-07321332 at a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritanovir) administrered as split dosing.*	N/A	• *Plasma PK parameters of PF-07321332:*
		  • *C_{max}, T_{max}, AUC_{last}*
		  • *If data permit, AUC_{inf}, $t_{½}$.*

2.2. Study Design

2.2.1. Overall Design

*The study will combine **PART-1:** single ascending dose (SAD), **PART-2:** multiple ascending dose (MAD, including optional Japanese cohort), **PART-3**: relative bioavailability and food effect cohort, **PART-4**: metabolism and excretion study, and **PART-5**: supratherapeutic exposure cohort. **PART-1** and **PART-2** are randomized, double-blind (participant and investigator blinded), sponsor open, placebo controlled, single and multiple dose escalation study. **PART-3** is a randomized open label study to evaluate relative bioavailability and food effect. **PART-4** is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. **PART-5** is a double-blind, sponsor open, randomized, cross-over study to evaluate safety and tolerability at supratherapeutic exposures to be conducted at NH CRU only.*

2.2.2. PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 12 participants planned (approximately 6 participants in each cohort), with 4-period cross-over in each cohort. Period 3 and 4 are optional periods which may be used to further explore PK at additional doses or PK in combination with ritonavir or relative bioavailability of a new formulation or food effect (high-fat high-calorie meal), etc, based on emerging safety, tolerability and PK assessments.

There will be a washout interval of ≥5 days between dosing to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator. The washout interval may be adjusted based on data emerging from previous cohorts/periods.

2.2.3. PART-2: MAD

*The first MAD cohort may start after a same total daily dose, which provides comparable or higher total daily exposure (24 h) in SAD than the projected total daily steady-state exposure (over 24 h) at the starting dose in MAD, is found safe and well tolerated in **PART-1** of the study. The proposed MAD study design will be parallel cohorts, with 10 days of dosing. **PART-2** will consist of approximately 2 to 5 cohorts including up to 3 optional cohorts (cohorts 5, 6 and 7) with approximately 6 participants in each cohort. Cohort 7 is an optional Japanese participants cohort.*

2.2.4. PART-3: RBA and Food effect

This cohort will be an open label, randomized, 3-period, 3-sequence cross-over single dose cohort evaluating the relative bioavailability of PF-07321332 tablet compared to PF-07321332 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07321332 tablet in healthy adult participants. A maximum of 18 participants may be enrolled in PART-3 of the study with approximately equal number of participants randomized to each sequence. There will be a wash-out period of at least 2 days between dosing in each period. Participants will be required to stay at the CRU until discharge in the last period. The washout interval may be adjusted based on data emerging from SAD and MAD cohorts.

2.2.5. PART-4: Metabolism and Excretion

This part will include a single cohort of approximately 6 male participants with at least 4 completers. All participants will receive 4 doses of 100 mg ritonavir as specified in the SoA. Each participant will receive a single dose of 300 mg of PF-07321332 on Day 1 0h along with 100 mg of ritonavir after at least 10h of fasting. The participants will be discharged on Day 11.

*In **PART-1** and **PART-2**, treatment sequences, actual doses, dose increments and dosing regimen may be adjusted, and intermediate or alternative dose levels may be substituted during the study based on emerging safety, tolerability, and PK data.*

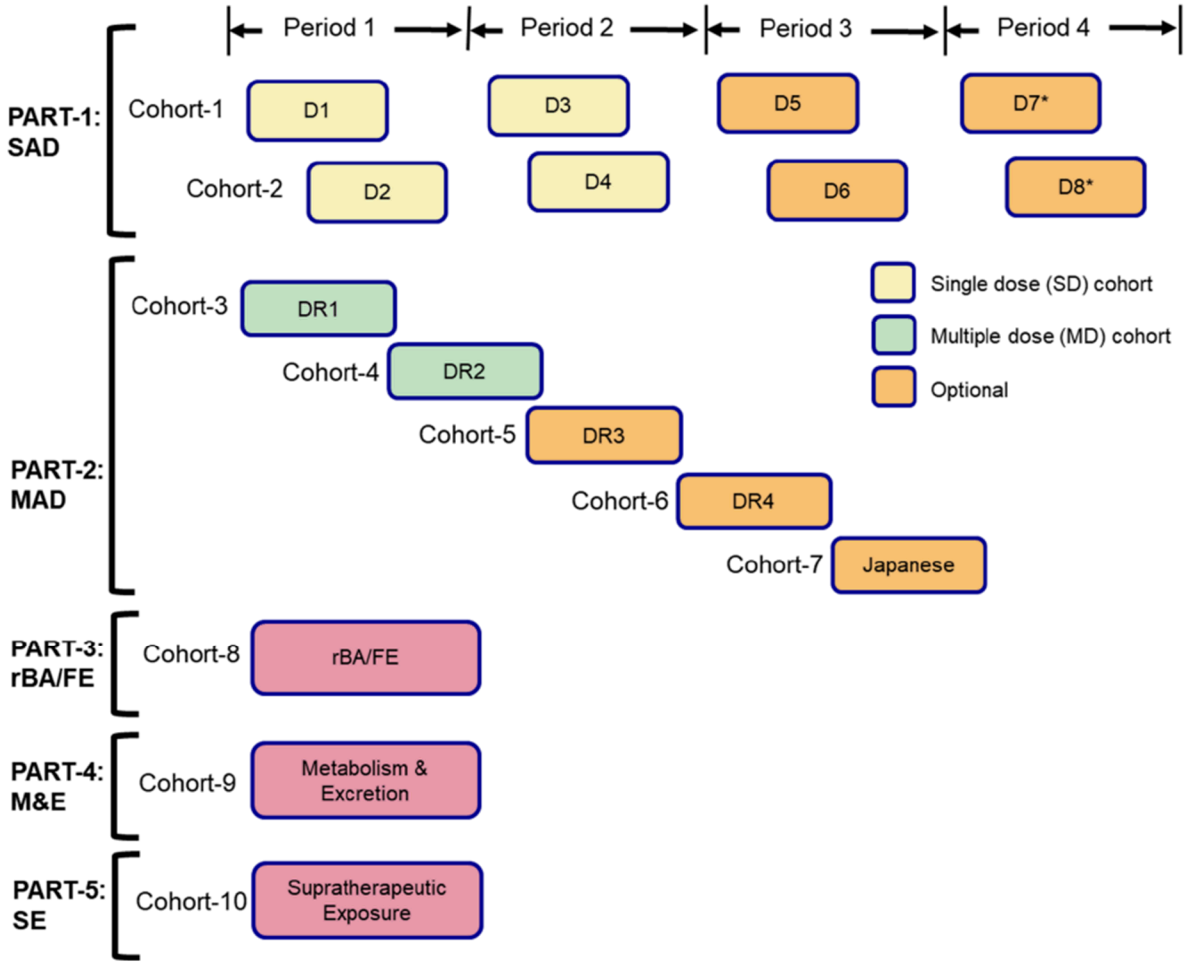
2.2.6. PART-5: Supratherapeutic Exposure (NH CRU only)

This cohort will include up to 12 participants in a 4-period (Periods 3 and 4 are optional), double-blind, sponsor-open, randomized, 2-sequence, cross-over design to explore safety, tolerability and PK at supratherpeutic exposure. For each period, participants will receive split dosing administration (3 doses) of PF-07321332 or placebo at short intervals (approximately 2 h of the previous dose) after at least 2 hours after the breakfast on Day 1. Baseline ECGs, vitals and safety labs will be collected before breakfast. The first 2 periods will be a cross-over where participants will be given PF-07321332 at 0, 2 and 4 hours at the dose of 750 mg (or placebo) with ritonavir. Periods 3 and 4 (if conducted) will only be conducted if supratherapeutic concentrations are not reached in Period 1. In periods 3 and 4 (if conducted) doses may be given up to 4 times for a total daily dose not exceeding 3000 mg, with or without food.

2.2.7. Number of Participants

*A total of up to 78 participants (12 in **PART-1: SAD**, up to 30 [with 2 cohorts and 3 optional cohorts] in **PART-2: MAD**, a maximum of 18 in **PART-3: Relative Bioavailability/Food Effect cohort,** 6 participants in **PART-4: Metabolism and Excretion cohort,** and up to 12 participants in **PART-5: Supratherapeutic Exposure**) are planned to be randomized in this study. At the discretion of the sponsor and investigator, participant who were enrolled in **PART-2** may be enrolled in **PART-5**.*

Figure 1. C4671001 Study Design



Optional dose levels in SAD/MAD may be used to explore higher doses or food effect or relative bioavailability or in combination with ritonavir (see more details in Section 4.1 of the protocol). Dosing with food may be done in one or more cohorts in SAD/MAD based on the emerging PK/safety data. **PART-4: Metabolism and Excretion (M&E) is an open-label single dose cohort (see more details in Section 4.1 of the protocol). **PART-5: supratherapeutic exposure (SE)** is a double-blind, sponsor-open, randomized, cross-over cohort (see more details in Section 4.1 of the protocol).*

SAD dose levels D1 to D8 and MAD dosing regimens DR1 to DR4 are listed in Table 9 and Table 10, respectively in Section 4.3 of the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

As listed in Section 2.1 the primary endpoints in PART-1, PART-2, and PART-5 are related to safety/tolerability and are described in Section 3.5.

The primary endpoints in PART-3 are the plasma PK endpoints which are described in Section 3.3.

The primary endpoints in PART-4 are percent recovery and cumulative recovery of drug-related material in urine, feces determined based on total administered dose. Percent recovery of drug-related material in urine and feces will be determined based on total administered dose.

3.2. Secondary Endpoint(s)

The secondary endpoints in PART-1, PART-2, PART-4 and PART-5 related to PK are described in Section 3.3. The secondary endpoints in PART-3 and PART-4 related to safety/tolerability are described in Section 3.5.

3.3. Other Endpoint(s)

3.3.1. Pharmacokinetic (PK) Endpoints

Blood and urine samples for the PK analysis of PF-07321332 will be taken according to the SoA given in the protocol.

The PK parameters of PF-07321332 to be derived (if data permit) from the concentration-time data using standard noncompartmental methods are defined in Table 2 (single oral dose) and Table 3 (multiple oral doses). Urine PF-07321332 PK parameters are described in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. Noncompartmental PK Parameters for PART-1: Single Ascending Doses, PART-3: Relative Bioavailability/Food Effect Cohort, PART-4: Metabolism and Excretion Cohort and PART-5: Supratherapeutic Exposure Cohort

Parameter	Analysis Scale	PF-07321332
AUC_{last}†	ln	D, A
AUC_{inf}*	ln	D, A
C_{max}	ln	D, A
T_{max}	R	D
$t_{½}$*	R	D
CL/F*§	ln	D
V_z/F*§	ln	D
AUC_{last}(dn) ‡	ln	D
AUC_{inf}(dn)* ‡	ln	D
C_{max}(dn) ‡	ln	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed), A=analysed
*=if data permits, dn = normalized to a 1mg PF-07321332 dose,
†=In PART-3, pre-dose (0h) sample from Periods 2 and 3 will also be considered as 48h PK sample for Periods 1 and 2, respectively,
‡=Not PART-4 or PART-5,
§=Not PART-5.

T_{last} will also be provided as a support parameter for AUC_{last}. T_{last} values will only be listed and not summarized.

Table 3. Noncompartmental PK Parameters for PART-2: Multiple Ascending Dose

Parameter	Analysis Scale	PF-07321332
Plasma		
AUC_{τ}	ln	D
C_{max}	ln	D
T_{max}	R	D
C_{min}	R	D
C_{av}	ln	D
R_{ac}	ln	D
$R_{ac,Cmax}$	ln	D
PTR	ln	D
CL/F	ln	D
$t_{½}$*	R	D
V_z/F*	ln	D
AUC_{τ}(dn)	ln	D
C_{max}(dn)	ln	D
Urine		
Ae_{τ}	R	D
Ae_{τ}%	R	D
CL_r	R	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed),
*=if data permits, dn = normalized to a 1mg PF-07321332 dose.

3.4. Baseline Variables

Baseline variables are those collected on Day 1 prior to dosing or before Day 1. Baseline for laboratory data, vital signs and ECG are defined in Sections 3.5.2, 3.5.3 and 3.5.4 respectively.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is 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 end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

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

3.5.2. Laboratory Data

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

For PART-1, PART-3 and PART-5, baseline will be the last pre-dose measurement prior to administration of PF-07321332 in each study period. For PART-2, baseline will be the last pre-dose measurement. For PART-4, baseline will be the last pre-dose measurement prior to administration of PF-07321332.

For PART-5, the pre-dose (Day -1) sample in Period 2 will also be used as a Day 5 (96h) sample.

To determine if there are any clinically significant laboratory abnormalities, the hematological, 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.

3.5.3. Vital Signs

Single supine blood pressure, respiratory rate, temperature and pulse measurements will be taken at times detailed in the SoA given in the protocol.

For PART-1, PART-3 and PART-5, baseline will be defined as the last pre-dose measurement prior to administration of PF-07321332 in each study period. For PART-2, baseline will be the last pre-dose measurement. For PART-4, baseline will be the last pre-dose measurement prior to administration of PF-07321332.

The following vital signs endpoints will be determined:

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

- The maximum decrease from baseline over all measurements taken post-dose for supine systolic and diastolic blood pressures and respiratory rate.

- The maximum increase from baseline over all measurements taken post-dose for supine pulse rate and temperature.

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

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

3.5.4. ECG

A 12-lead ECG will be obtained on all participants at screening. A triplicate measurement will be performed in PART-1, PART-2 and PART-5, and a single measurement in PART-3 and PART-4.

12-lead ECGs will be recorded on all participants at times detailed in the SoA given in the protocol. Triplicate measurements will be performed in PART-1, PART-2 and PART-5, and single measurements in PART-3 and PART-4. The QT, heart rate, QTcF, PR and QRS will be recorded at each assessment time.

The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. For PART-1 and PART-5, baseline will be defined as the average of the triplicate measurements prior to administration of PF-07321332 in each study period. For PART-2, baseline will be defined as the average of the triplicate measurements prior to administration of PF-07321332 on Day 1. For PART-3, baseline will be defined the last measurement prior to administration of PF-07321332 in each study period. For PART-4, baseline will be defined as the last measurement prior to administration of PF-07321332.

The following ECG endpoints will be determined:

- Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex.

- The maximum absolute value (post-dose) will be calculated for QTcF, PR and QRS.

- The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each triplicate-average post-dose measurement to give the change from baseline. The

maximum of these values over the respective period will then be selected, except in the case where a 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.

The study part referred to below can be either **PART-1: SAD**, **PART-2: MAD**, **PART-3: Relative Bioavailability/Food Effect cohort**, **PART-4: Metabolism and Excretion cohort**, or **PART-5: Supratherapeutic Exposure cohort**, unless otherwise specified.

Population	Description
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Evaluable	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given part of the study.*
Safety	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.*
PK Parameter Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.*

Population	Description
Excretion Analysis Set	*In **PART-4**, excretion analysis population will be defined by evaluable participants who have received 1 dose of PF-07321332 and who have completed drug related material concentration (urinary and fecal) data and who had no protocol deviations that may have affected the mass balance analysis.*

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.

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, cv%, median, minimum and maximum values.

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

5.2.2. Analyses for Categorical Endpoints

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

5.3. Methods to Manage Missing Data

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

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 (LLQ).

For PK summary tables and plots of mean/median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

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

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 dose with ≥3 evaluable measurements.

If an individual participant 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

Separate tables will be produced for **PART-1: SAD, PART-2: MAD, PART-3: Relative Bioavailability/Food Effect Cohort**, **PART-4: Metabolism and Excretion Cohort and PART-5: Supratherapeutic Exposure Cohort**, unless otherwise specified. Placebo and Placebo + Ritonavir will be separate treatment groups. In Part-2, Japanese and non-Japanese will be separate treatment groups.

6.1. Primary Endpoint(s)

The primary endpoints in PART-1, PART-2 and PART-5 are related to safety/tolerability and their analyses are described Section 6.6.

The primary endpoints in PART-3 are the plasma PK endpoints whose analyses are described in Section 6.2.

The primary endpoints in PART-4 are percent recovery and cumulative recovery of drug-related material in urine, feces based on total administered dose. This will be calculated and reported separately.

6.2. Secondary Endpoint(s)

The secondary endpoints in **PART-1**, **PART-2**, **PART-4** and **PART-5**, as well as the primary endpoints in **PART-3**, are related to PK and are described herein.

No formal inferential statistics will be applied to the plasma PK data apart from the comparisons of formulation and food effect in either **PART-1** or **PART-3**

The PK parameters detailed in Section 3.3.1 will be listed and summarized for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3. Each PK parameter will be summarized by matrix (plasma or urine), treatment and dose. Each summary will include the set of summary statistics as specified in

Table 4. Summaries will be performed separately for PART-1, PART-2, PART-3, PART-4 and PART-5.

Table 4. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CL/F, V_z/F, AUC_{last}(dn), AUC_{inf} (dn), C_{max}(dn), AUC_{τ}, C_{min}, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, AUC_{τ} (dn), Ae_{τ}, Ae_{τ}%, and CL_r	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, standard deviation, minimum, maximum.

To assess the relationship between the PK parameters and dose, dose normalized C_{max}, AUC_{last}, and AUC_{inf} (**PART-1**) and C_{max} and AUC_{τ} (**PART-2**) of PF-07321332 will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. In Part-2, the data from the Japanese subjects will be identified by different symbols/colours. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented. All dose normalized parameters will be listed along with other individual PK parameters.

Supporting data from the estimation of $t_{½}$ will be listed by treatment and dose where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. These data may be included in the CSR.

Presentations for PF-07321332 concentrations will be presented using participants in the PK Concentration Set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by participant ID, dose, matrix and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- a summary of concentrations by dose and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv),

minimum, maximum and the number of concentrations above the lower limit of quantification.

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

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long PF-07321332 concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

For **PART-2**, urine amounts of PF-07321332 as listed in Table 3 will be listed and summarized descriptively, if data permit.

To assess any effect of food/formulation in **PART-3**, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07321332 will be analyzed using a mixed effects model with sequence, period and treatment included as a fixed effect and participant nested within sequence as a random effect. If performed, to assess any effect of food/formulation in **PART-1**, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07321332 will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect using participants with data from both periods only. The Kenward-Roger adjustment for the degrees of freedom will be used. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for these differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for these ratios.

The following comparisons will be made:

Comparison	Test	Reference
Formulation	PF-07321332 tablet formulation in fasted state (B)	PF-07321332 oral suspension in fasted state (A)

Food Effect	PF-07321332 tablet formulation in fed (high fat meal) state (C)	PF-07321332 tablet formulation in fasted state (B)

6.3. Other Endpoints

CCI [redacted]

Qualitative characterization of metabolites of PF-07321332, quantitative excretion of drug related material using ^{19}F-NMR spectroscopy, metabolic profiling/identification and determination of relative abundance of PF-07321332 and its metabolites will be analysed separately and maybe included in the CSR in an appendix. Exploring of PK by microsampling is an exploratory endpoint 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

6.5.1. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition by treatment. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.2. Demographic Data

Demographic data (age, biological sex, race, ethnicity, weight, body mass index and height) will be summarised by cohort for PART-1, PART-3 and PART-5, by treatment for PART-2 and PART-4, and overall (if applicable) in accordance with the sponsor reporting standards.

6.5.3. Concomitant Medications and Nondrug Treatments

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

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

In all 5 parts of the study, all safety analyses will be performed on the Safety Analysis Set.

6.6.1. Adverse Events

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

6.6.2. 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.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be plotted against time post-dose. Each part will have its own output with 1 line for each treatment. Placebo will be pooled in the plots for PART-1, PART-2 and PART-5, although the Japanese placebo in PART-2 will be treated as a separate treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine systolic and diastolic blood pressures and respiratory rate and maximum increase from baseline for supine pulse rate and temperature will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and changes from baseline for supine 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 time points will be counted in these categorical summaries.

6.6.4. ECG

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment and time post-dose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. Each part will have its own output with 1 line for each treatment. Placebo will be pooled in the plots for PART-1, PART-2 and PART-5, although the Japanese placebo in PART-2 will be treated as a separate treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations of PF-07321332. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment.

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

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTcF these correspond to the Pfizer Guidance in Section 8). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose time points will be counted in these categorical summaries.

Listings of participants with any single post-dose value >500msec will also be produced for QTcF.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

7.2. Interim Analyses and Summaries

N/A

8. REFERENCES

Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018

APPENDICES

Appendix 1. 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