Protocol C3591036

A PHASE 3, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF CEFTAZIDIME-AVIBACTAM (PF-06947386) PLUS METRONIDAZOLE IN JAPANESE ADULT PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTION REQUIRING HOSPITALIZATION

Statistical Analysis Plan
(SAP)

Version: 3

Date: 21 Sep 2022

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 Jun 2021	Original 19 Apr 2021	N/A	N/A
2 11 Jul 2022	Amendment 1 21 July 2021	Clarified the details	Section 3.4 Added definition of baseline.
		Clarified the details	Section 3.5.1 Updated the definition of TEAE because time is not collected in the C3591036 study.
		Clarified the details	Section 4 • Added clarification that CE, ME, and eME analysis sets are prepared for each EOT, TOC, and LFU. • Added clarification that Sepsis patients subset and Sepsis evaluable patients subset are based on eME at TOC analysis population.
		CCI [redacted]	[redacted]
		Updated the details	Section 5.3 Added details of the method to manage missing data for clinical and microbiological response assessments.
		Clarified the details	Section 5.4, Section 5.5 Added definition of susceptibility criteria for CAZ-AVI and ceftazidime resistance.
		Clarified the details	Section 6 Clarified analysis populations used for each analysis.
		Updated the analysis	Section 6 Deleted analyses regarding reason for clinical failure and indeterminate clinical response.
		Updated the analysis	Section 6 Updated and clarified the details for listing.
		Updated the analysis	Section 6.2.5 Updated and clarified the details for pharmacokinetic analysis.

[redacted]

[redacted]

		CCI [redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		Updated the analysis	Section 6.4 Added the analysis regarding forest plots.
		Updated the analysis	Section 6.5.1 Added analyses regarding MIC for CAZ-AVI and other drugs for pathogens isolated in this study, if available.
		Updated the analysis	Section 6.5.2 Deleted the analysis regarding the reasons for exclusion from analysis sets.
		Clarified the details	Section 6.5.3 • Deleted the analysis regarding IV infusions and individual component of study therapy (Total number of IV infusions). • Added definition of study treatment compliance.
		Updated the analysis	Section 6.6.1 Added the analysis regarding adverse events of special interest.
		Updated the analysis	Section 6.6.3 • Added the analysis regarding change from baseline. • Added the analysis for box and whisker plots.
		Overall	Minor edits for the description maintenance.
3 21 Sep 2022	Amendment 1 21 July 2021	Clarified the details	Section 5.3.1 Added description on handling of concentrations below the limit of qualification.
		Clarified the details	Section 6 Added clarification that assessment by the adjudication committee will prevail when

			both investigator and the adjudication committee assessment are available.
		Clarified the details	Section 6 Clarified the definition of all patients (updated “all patients” to “all enrolled patients”).
		Updated the analysis	Section 6.2.2 Deleted the analysis regarding emergent infections for eME at TOC and ME at TOC analysis sets.
		Updated the analysis	Section 6.2.3 Added description on the listing for microbiological culture results.
		Updated the analysis	Section 6.2.5 Updated parameters for the summay of the plasma concentration as same as Section 5.2.2.
		CCI [redacted]	[redacted]
		Updated the analysis	Section 6.4 Deleted the subset analysis regarding clinical cure rate at EOT, TOC, and LFU visits for MITT and mMITT analysis sets.
		Updated the analysis	Section 6.4 Updated the subset analyses for sepsis patients subset and sepsis evaluable patients subset.
		Updated the analysis	Section 6.5.1 Deleted the analysis regarding demographic characteristics, patient characteristics, and disease characteristics for mMITT and CE at TOC analysis sets. Updated the analysis for the prior systemic antibiotics use from “72 hours before enrollment” to “3 days before enrollment including the day of enrollment”, and added the analysis for the secondary diagnosis. Deleted the analyses regarding pathogens for ME at TOC analysis set.
		Updated the analysis	Section 6.5.4

			Deleted the analysis regarding prior systemic antibiotic medications for CE at TOC analysis set. Added description on the analysis for prior medications other than prior systemic antibiotic medications.
		Updated the analysis	Section 6.6.1 Added description on the listings for the event terms for adverse events of special interest and medication errors.
		Updated the analysis	Section 6.6.2 Added description on the listings for Hy's Law values.
		Updated the analysis	Section 6.6.3 Deleted weight and BMI from box and whisker plots. Changed the analysis set for the listing from all patients to the safety population.
		Updated the analysis	Section 6.6.4 Added description on the listings for electrocardiogram data.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3591036. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To assess the efficacy of PF-06947386 plus metronidazole	• Estimand 1: the primary estimand of the primary endpoint The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of clinical response in patients with cIAI. A composite estimand strategy will be used. Intercurrent events of death where cIAI is clearly noncontributory etc. will be regarded as indeterminate clinical response. Intercurrent events of death related to intra-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Appendix 2.1. All data after	• Clinical response at the TOC visit

Objectives	Estimands	Endpoints
	intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be considered. All data after other intercurrent events that affect the clinical assessment will not be considered. Proportion of participants with clinical cure will be calculated. • Estimand 2: the supportive estimand of the primary endpoint The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of clinical response in patients with cIAI. A composite estimand strategy will be used. Intercurrent events of death where cIAI is clearly noncontributory etc. will be regarded as indeterminate clinical response. Intercurrent events of death related to intra-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Appendix 2.1. Proportion of participants with clinical cure will be calculated.	
	• Estimand 3: the supportive estimand of the primary endpoint The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of clinical response in patients with cIAI who have ≥1 baseline pathogens. A composite estimand strategy will be used. Intercurrent events of death where cIAI is clearly noncontributory etc. will be regarded as indeterminate clinical response. Intercurrent events of death related to intra-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Appendix 2.1. Proportion of participants with clinical cure will be calculated. • Estimand 4: the supportive estimand of the primary endpoint The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of clinical response in patients with cIAI who have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture regardless of susceptibility. A composite estimand strategy will be used. Intercurrent events of death where cIAI is clearly noncontributory etc. will be regarded as indeterminate clinical response. Intercurrent events of death related to intra-	

Objectives	Estimands	Endpoints
	abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Appendix 2.1. All data after intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be considered. All data after other intercurrent events that affect the clinical assessment will not be considered. Proportion of participants with clinical cure will be calculated. • Estimand 5: the supportive estimand of the primary endpoint The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of clinical response in patients with cIAI who have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture that is susceptible. A composite estimand strategy will be used. Intercurrent events of death where cIAI is clearly noncontributory etc. will be regarded as indeterminate clinical response. Intercurrent events of death related to intra-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Appendix 2.1. All data after intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be considered. All data after other intercurrent events that affect the clinical assessment will not be considered. Proportion of participants with clinical cure will be calculated.	
Secondary:	**Secondary:**	**Secondary:**
• To determine the efficacy of PF-06947386 plus metronidazole • To determine the per-patient microbiological response of PF-06947386 plus metronidazole	• Estimands 6 - 10: the estimands of the secondary endpoints Same as Estimands 1 - 5 • Estimand 11: the estimand of the secondary endpoints The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of microbiological response in patients with cIAI who have ≥1 baseline pathogens. A composite estimand strategy will be used. Intercurrent events of lost to follow-up and death where cIAI is clearly noncontributory etc. will be regarded as indeterminate microbiological response. For details, see Appendix 2.2. Proportion of participants with favorable microbiological response will be calculated.	• Clinical response at EOT, and LFU visits • Per-patient microbiological response at EOT, TOC, and LFU visits

Objectives	Estimands	Endpoints
	• Estimand 12: the estimand of the secondary endpoints The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of microbiological response in patients with cIAI who have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture regardless of susceptibility. A composite estimand strategy will be used. Intercurrent events of lost to follow-up and death where cIAI is clearly noncontributory etc. will be regarded as indeterminate microbiological response. For details, see Appendix 2.2. All data after intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be considered. All data after other intercurrent events that affect the microbiological assessment will not be considered. Proportion of participants with favorable microbiological response will be calculated. • Estimand 13: the estimand of the secondary endpoints The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in terms of microbiological response in patients with cIAI who have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture that is susceptible. A composite estimand strategy will be used. Intercurrent events of lost to follow-up and death where cIAI is clearly noncontributory etc. will be regarded as indeterminate microbiological response. For details, see Appendix 2.2. All data after intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be considered. All data after other intercurrent events that affect the microbiological assessment will not be considered. Proportion of participants with favorable microbiological response will be calculated.	
• To determine the per-pathogen microbiological response of PF-06947386 plus metronidazole	• Estimands 14 - 16: the estimands of the secondary endpoints Same as Estimands 11 - 13	• Per-pathogen microbiological response at EOT, TOC, and LFU visits • Per-pathogen microbiological response at EOT, TOC, and LFU visits by MIC categories
• To evaluate the safety and tolerability profile of PF-06947386 plus metronidazole in	N/A	• AEs and SAEs, all cause mortality, reasons for discontinuations of

Objectives	Estimands	Endpoints
the treatment of patients with cIAIs		IV study intervention and study, vital sign measurements, and potentially clinically significant changes in laboratory parameters during the entire study
• To evaluate the pharmacokinetics of the individual components of PF-06947386 in patients with cIAIs	N/A	• Ceftazidime and avibactam plasma concentrations by nominal sampling window
• To investigate safety and efficacy for patients with sepsis (if available)	N/A	• Selected efficacy and safety endpoints as described above
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

2.1.1. Primary Estimand(s)

See section 2.1 (Estimand 1 is the primary estimand of the primary endpoint and Estimands 2-5 are the supportive estimands of the primary endpoint).

2.1.2. Secondary Estimand(s)

See section 2.1 (Estimands 6-16 are the estimands of the secondary endpoints).

2.1.3. Additional Estimand(s)

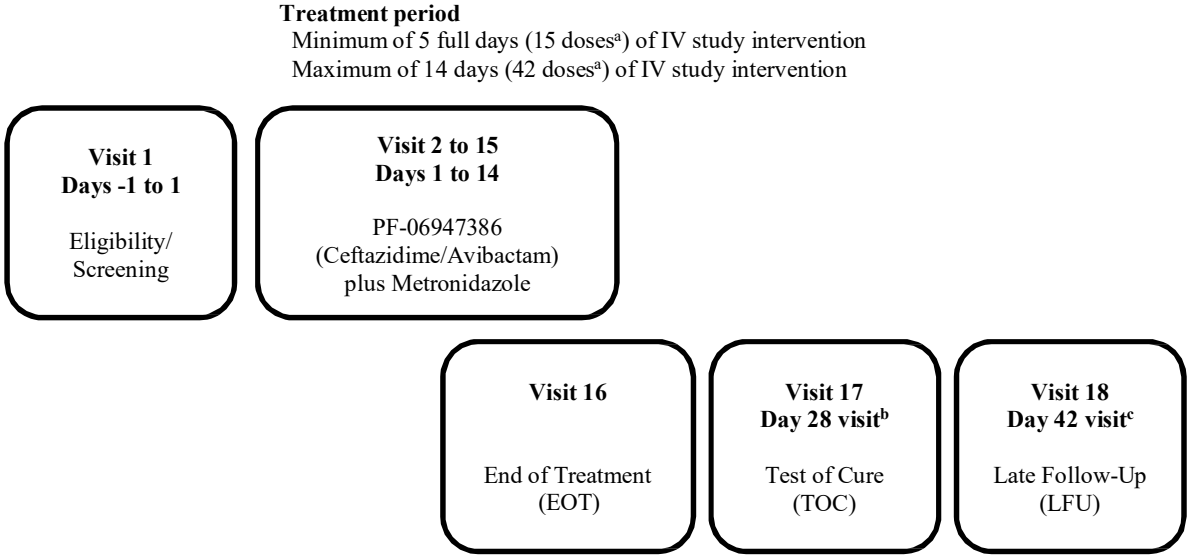
Not Applicable

2.2. Study Design

Study C3591036 will assess the efficacy and safety of PF-06947386 in Japanese hospitalized participants with cIAI. This is a multicenter, open-label, single-arm study. The study will have a maximum duration of approximately 6 weeks for each participant. This includes a 5-14 days of IV study period, TOC visit at Day 28, and LFU visit at Day 42. The study outline is shown in Figure 1.

Eligible participants with CrCL >50 mL/min will be given an IV dose of 2.5 g PF-06947386 (ceftazidime 2.0 g/avibactam 0.5 g) q8h with infusion time of 2 hours for 5-14 days. For participants enrolled into the study whose CrCL drops to ≤50 mL/min while on IV investigational drug therapy, dosage adjustment is required depending on the degree of renal impairment based on the CrCL value (protocol Section 6). All eligible participants will receive metronidazole (0.5 g) intravenously with an infusion duration of 60 minutes. When both PF-06947386 and metronidazole are administered at the same time, metronidazole will be administered immediately after administration of PF-06947386.

Figure 1. Study Outline



a. For participants with normal renal function and participants with mild renal impairment.
b. If it is not possible to perform the TOC visit on study Day 28 (eg, the participant is on holiday), the allowed visit window is Day 28 to 35.
c. If it is not possible to perform the LFU visit on study Day 42 (eg, the participant is on holiday), the allowed visit window is Day 42 to 49.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint for the study is clinical response at the TOC visit.

The assessment by the adjudication committee will be used.

3.2. Secondary Endpoint(s)

The secondary endpoints for the study are as follows.

- Clinical response at EOT and LFU visits
- Per-patient microbiological response at EOT, TOC, and LFU visits
- Per-pathogen microbiological response at EOT, TOC, and LFU visits
- Per-pathogen microbiological response at EOT, TOC, and LFU visits by MIC categories
- Ceftazidime and avibactam plasma concentrations by nominal sampling window
- For patients with sepsis, selected efficacy and safety endpoints from endpoints for the overall population

The assessment by the adjudication committee will be used for the clinical and microbiological responses.

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3.4. Baseline Variables

The following baseline variables will be assessed. Baseline variables will be those collected on Day 1 prior to the initial administration or the last measurement obtained as the screening assessment. In cases where there are multiple measurements for the same assessment, the

measurement obtained at a timing closest to the initial administration will be defined as the baseline variable.

- APACHE II score
- Demographics (age, sex, ethnicity, race)
- Medical and surgical history
- Abdominal signs and symptoms examination; wound examination
- Temperature
- Pulse rate, blood pressure, respiratory rate
- Heart rate
- estimated CrCl
- Height, weight, body mass index (BMI)
- Imaging test (when available)
- Description of operative procedure [from initial qualifying procedure {performed within 24 hours of entry for preoperative enrollment (see protocol Section 5.1, inclusion criterion 3)}]
- Prior and concomitant treatment/antibiotics
- Blood culture
- Culture of abdominal infection site [at initial qualifying procedure {performed within 24 hours of entry for preoperative enrollment (see protocol Section 5.1, inclusion criterion 3)}]

3.5. Safety Endpoints

3.5.1. Adverse Events

The MedDRA adverse event dictionary will be used to map Adverse Event (AE) to Preferred Terms (PTs) and System Organ Classes (SOCs).

A Treatment Emergent Adverse Event (TEAE) is defined as an AE that emerges or worsens during the effective duration of treatment. All events that start on or after the first dosing day will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

3.5.2. Laboratory Data

The following safety laboratory tests will be performed at times defined in the SoA section of the protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Results will be reported by the local laboratory.

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Dipstick Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Eosinophils (Abs, %) Lymphocytes (Abs, %) Monocytes (Abs, %) Neutrophils (Abs, %) Neutrophils, immature (Abs, %) Basophils (Abs, %)	BUN Creatinine Glucose (non-fasting) Calcium Sodium Potassium Chloride AST ALT GGT Bilirubin (total and direct) Alkaline phosphatase Albumin Total protein CRP	Glucose (qual) Protein (qual) Blood (qual)	FSH[a] β -hCG[b]

a. For confirmation of postmenopausal status only.
b. At Screening, serum β-hCG must be performed as part of screening/eligibility. If the results of β-hCG are not available prior to dosing of study intervention, a patient may begin therapy on the basis of a negative urine β-hCG, but a serum test must still be obtained. At time points other than Screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL.

3.5.3. Other Safety Endpoints

Vital signs, weight, and BMI will be evaluated.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Analysis Set	Description
MITT analysis set	The MITT analysis set includes all enrolled participants who: 1. Meet the disease definition of cIAI (see protocol Section 5.1, inclusion criterion 3).

	2. Receive any amount of study drug.
mMITT analysis set	The mMITT analysis set includes all enrolled participants who: 1. Meet the disease definition of cIAI (see protocol Section 5.1, inclusion criterion 3). 2. Receive any amount of study drug. 3. Have at least 1 etiologic pathogen identified at study entry (regardless of isolate susceptibilities). Participants with a bacterial species typically not expected to respond to the study drug (eg, Acinetobacter spp., Stenotrophomonas spp.) are excluded (ie, if the study drug is considered inadequate to treat the pathogen in most clinical circumstances).
CE analysis set*	Participants are included who meet the following criteria: 1. Have an appropriate diagnosis of cIAI (see protocol Section 5.1, inclusion criterion 3). As an exception, participants with a bacterial species typically not expected to respond to the study drug (eg, Acinetobacter spp., Stenotrophomonas spp.) are excluded. 2. EITHER (a) Receive therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered OR (b) Receive therapy <48 hours before discontinuing treatment due to an AE. 3. Is evaluated with a clinical response of cure or failure. Participants with a clinical response of failure at a previous visit are not excluded from subsequent timepoints for visits that are out of window. 4. Have no important protocol deviations that will affect assessment of efficacy at the relevant timepoint. 5. Do not receive any prior antibiotics other than protocol-allowed antibiotics with specified duration in protocol

	Section 5.2, exclusion criterion 22. Determination of duration in some circumstances is done manually. 6. Do not receive concomitant antibiotic therapy with potential activity against any of the baseline aerobic pathogens between the time of first IV infusion and the time of the relevant timepoint culture, respectively, except for protocol-allowed antibiotics for the coverage of Enterococcus spp. and MRSA. This does not include participants who have failed and require additional antibiotic therapy. Topical antibacterials and antifungals are permitted except that they are not being applied to the surgical site. (Note that if topical antibacterials and antifungals are applied to the surgical site this does not lead to exclusion from the CE analysis set). Potential activity against any of the baseline aerobic pathogens is determined by manual review by comparing the susceptibility profile of the baseline aerobic pathogens to the antibiotic received. When no baseline pathogens are identified, a conservative approach is taken and the patient is excluded from the CE analysis set. 7. Consider to have adequate initial infection source control.
ME analysis set*	Participants are included who meet the following criteria: 1. Include in a subset of CE participants. 2. Have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture that is susceptible.
eME analysis set*	Participants are included who meet the following criteria: 1. Include in a subset of CE participants. 2. Have at least 1 Gram-negative aerobic pathogen in the initial/prestudy culture regardless of susceptibility.
Sepsis patients subset**	1. Include in a subset of eME participants. 2. Satisfy both clinical and microbiological criteria

	Clinical: Total score ≥ 2 in SOFA for ICU patients, 2 items or more in qSOFA for non-ICU patients (protocol Section 10.7) at Baseline Microbiological: The most relevant pathogens (ie, aerobic Gram-negative bacteria -either Enterobacterales or aerobic Gram-negative pathogens other than Enterobacterales) isolated from the blood at Baseline regardless of susceptibility.
Sepsis evaluable patients subset**	1. Include in a subset of eME participants. 2. Satisfy both clinical and microbiological criteria Clinical: Satisfy at least one following criteria at Baseline. 1) body temperature ≥38°C or <36°C, 2) WBC >12000 cells/mm^3 or <4000 cells/mm^3, or immature neutrophil >10%, 3) heart rate >90 bpm, 4) systolic blood pressure <90 mmHg, 5) CRP ≥20 mg/dL Microbiological: The most relevant pathogens (ie, aerobic Gram-negative bacteria -either Enterobacterales or aerobic Gram-negative pathogens other than Enterobacterales) isolated from the blood at Baseline regardless of susceptibility.
Safety analysis set	The Safety analysis set includes all participants who receive any amount of IV study intervention.
PK analysis set	The PK analysis set includes all participants who have at least 1 plasma concentration data value available for either CAZ or AVI.

*: Analysis population will include at EOT, TOC, and LFU.
**: Analysis population for eME at TOC will be used.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

In this study, no formal hypothesis testing will be conducted.

As an efficacy evaluation criterion, it will be confirmed that the point estimate of proportion of patients with clinical cure at TOC visit in the CE analysis set (the primary analysis) is ≥78%.

5.2. General Methods

Descriptive summaries will be provided where appropriate for each of the primary, secondary, and CCI [redacted]. In general, summaries will be presented for the MITT and mMITT analysis sets, and the ME, eME, and CE analysis sets at the appropriate visit.

5.2.1. Analyses for Binary Endpoints

Bianry variable summaries will include as appropriate the number of patients/pathogens, frequency, and proportion and the 95% confidence interval (CI) calculated by Clopper-Pearson method. In general, the denominator for each proportion calculation is based upon the total number of patients/pathogens in the study population.

5.2.2. Analyses for Continuous Endpoints

Continuous and quantitative variable summaries will include as appropriate the number of patients/pathogens, mean, SD, median, and ranges (minimum and maximum). CCI [redacted] Plasma concentrations will be summarized by the number of patients, mean, CV, median, and ranges (minimum and maximum).

5.2.3. Analyses for Categorical Endpoints

Categorical and qualitative variable summaries will include as appropriate the frequency and percent of patients/pathogens who are in each category. In general, the denominator for each percent calculation is based upon the total number of patients/pathogens in the study population.

5.2.4. Analyses for Time-to-Event Endpoints

Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method.

5.3. Methods to Manage Missing Data

Clinical and microbiological response assessment results at early termination will be imputed to the nearest scheduled assessment. In the case of non-responders (failure or unfavorable), assessment results for all subsequent visits will be handled as non-responders. Similarly, in the case of indeterminate, assessment results for all subsequent visits will be handled as indeterminate. Such imputed data will be annotated in the relevant listings.

For the other endpoints, in general, missing data will not be imputed.

5.3.1. Concentrations Below the Limit of Quantification

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where "LLQ" will be replaced with the value for the lower limit of quantification (LLQ).

5.4. Definition of susceptibility criteria for Ceftazidime-avibactam

When baseline pathogens as determined by the adjudication committee meet the following criteria, the MIC values of each baseline pathogen will be categorized as Susceptible, Intermediate, or Resistant according to the Clinical and Laboratory Standards Institute (CLSI) criteria[1] (Table 3). Because MIC values by the central laboratory are reported as ceftazidime concentration only, classification will be performed based on the values of ceftazidime concentration in the following table.

Table 3. Definition of susceptibility criteria for Ceftazidime-avibactam

	Interpretative categories and MIC break points, µg/mL		
	Susceptible	**Intermediate**	**Resistant**
Enterobacterales	≤8/4	–	≥16/4
Pseudomonas aeruginosa	≤8/4	–	≥16/4

Before and after "/" are Ceftazidime concentration and Avibactam concentration, respectively.

5.5. Definition of Ceftazidime resistance

Ceftazidime resistance is defined as those bacterial isolates whose susceptibility-to-ceftazidime results are intermediate or resistant using CLSI criteria[1] (ceftazidime minimum inhibitory concentrations ≥8 µg/mL for Enterobacterales and ≥16 µg/mL for *Pseudomonas aeruginosa*).

Table 4. Definition of susceptibility criteria for Ceftazidime

	Interpretative categories and MIC break points, µg/mL		
	Susceptible	**Intermediate**	**Resistant**
Enterobacterales	≤4	8	≥16
Pseudomonas aeruginosa	≤8	16	≥32

6. ANALYSES AND SUMMARIES

When both investigator and the adjudication committee assessment are available, the assessment by the adjudication committee will be summarized and listed.

6.1. Primary Endpoint(s)

6.1.1. Clinical response at the TOC visit

6.1.1.1. Main Analysis

The number of patients, frequency, and proportion and the 95% CI will be calculated for the CE at TOC analysis set.

6.1.1.2. Sensitivity/Supplementary Analyses

The same summary as the main analysis will be generated on the MITT, mMITT, ME at TOC, and eME at TOC analysis sets.

Clinical response will be listed for all enrolled patients.

6.2. Secondary Endpoint(s)

6.2.1. Clinical response at EOT and LFU visits

The number of patients, frequency, and proportion and the 95% CI will be calculated for the MITT, mMITT, CE (CE at EOT and CE at LFU), ME (ME at EOT and ME at LFU), and eME (eME at EOT and eME at LFU) analysis sets.

Clinical response will be listed for all enrolled patients.

6.2.2. Per-patient microbiological response at EOT, TOC, and LFU visits

The number of patients, frequency, and proportion and the 95% CI (calculate when $N \geq 10$) will be calculated for the mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU) analysis sets. Patients with "Indeterminate" are not included in the denominator. Patients with superinfection or new infection assessment will be handled as "Persist" based on the Guideline for Clinical Evaluation of Antibacterial Drugs[2].

Per-patient microbiological response will be listed for all enrolled patients.

Emergent infections (the number of patients with a superinfection, and the number of patients with a new infection) will be summarized for the mMITT analysis set. For the definition of emergent infections, see Appendix 2.3.

6.2.3. Per-pathogen microbiological response at EOT, TOC, and LFU visits

The number of patients/pathogens, frequency, and proportion will be calculated for the mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU) analysis sets. Patients with "Indeterminate" are not included in the denominator.

Per-pathogen microbiological response assessments at EOT, TOC, and LFU visits will be summarized for the mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU) analysis sets.

Microbiological culture results will be listed for all enrolled patients.

6.2.4. Per-pathogen microbiological response at EOT, TOC, and LFU visits by MIC categories

The number of patients/pathogens, frequency, and proportion will be calculated for the mMITT, ME, and eME analysis sets. Patients with "Indeterminate" are not included in the denominator. MIC categories will be grouped by susceptibility (Susceptible, Intermediate, Resistant) to CAZ-AVI for specific pathogens (Section 5.4).

Per-pathogen microbiological response assessments will be listed for all enrolled patients. MIC categories and susceptibility (Susceptible, Intermediate, Resistant) to CAZ-AVI and ceftazidime (Section 5.4 and Section 5.5) will be added as well as drug-resistance (AmpC, ESBL, and Carbapenemase) and genotype for specific pathogens.

6.2.5. Pharmacokinetic Analysis

The PK analysis set defined in Section 4 will be used for all PK analysis. Nominal sample window is defined as 1) anytime from 15 minutes prior to stopping until 15 minutes after stopping PF-06947386 infusion, 2) anytime between 30 minutes and 90 minutes after stopping PF-06947386 infusion, and 3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping PF-06947386 infusion but before the next dose. Blood samples for PK analyses are to be collected on Day 3 and Day 4.

A listing of ceftazidime and avibactam plasma concentrations at the nominal sampling windows and actual times by patients will be provided. The plasma concentration will be summarized by nominal sampling time window using appropriate descriptive statistics [e.g., the number of patients, mean, CV, median, and ranges (minimum and maximum)].

Individual plasma concentration profiles will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all enrolled patients on a single plot for each analyte.

An appropriate population PK model will be used for the purpose of estimating PK parameters and the time above MIC. Additional details of the methodology will be captured in a separate modeling plan and the results will also be reported separately.

CCI [redacted]

CCI

[redacted]

6.4. Subset Analyses

Clinical cure rate at EOT, TOC, and LFU visits will be calculated by baseline patient characteristics and baseline demographics characteristic subgroup, by baseline disease characteristic subgroup, and by prior systemic antibiotic subgroup for the CE at TOC analysis set. Regarding these analyses, forest plots will be displayed graphically for the CE at TOC analysis set.

Clinical cure rate at EOT, TOC, and LFU visits will be calculated by baseline pathogen and its MIC categories for the mMITT, ME at TOC, and eME at TOC analysis sets. MIC categories will be grouped by susceptibility (Section 5.4) to CAZ-AVI for specific pathogens.

Clinical cure rate at EOT, TOC, and LFU visits will be calculated by drug-resistance (AmpC, ESBL, and Carbapenemase) and genotype of baseline pathogen for the mMITT, ME at TOC, and eME at TOC analysis sets.

Per-pathogen microbiological response at EOT, TOC, and LFU visits will be calculated by drug-resistance (AmpC, ESBL, and Carbapenemase) and genotype of baseline pathogen for the mMITT, ME at TOC, and eME at TOC analysis sets.

Clinical cure rate at EOT, TOC, and LFU visits will be calculated for patients infected by ceftazidime-resistant Gram-negative pathogen (Intermediate or Resistant by CLSI criteria, Section 5.5) for the mMITT, ME at TOC, and eME at TOC analysis sets.

Per-patient microbiological response at EOT, TOC, and LFU visits will be calculated in patients infected by ceftazidime-resistant aerobic Gram-negative pathogen (Intermediate or Resistant by CLSI criteria, Section 5.5) for the mMITT, ME at TOC, and eME at TOC analysis sets.

Microbiological response per ceftazidime-resistant aerobic Gram-negative pathogen (Intermediate or Resistant by CLSI criteria, Section 5.5) at EOT, TOC, and LFU visits will be calculated for the mMITT, ME at TOC, and eME at TOC analysis set.

[redacted]

[redacted]

For sepsis patients subset and sepsis evaluable patients subset described in section 4, efficacy analyses of the primary endpoint described in section 6.1 and the secondary endpoints described in section 6.2 including PK analysis will be performed. However, analysis for emergent infections in section 6.2.2 will not be performed. Clinical cure rate at EOT, TOC, and LFU visits will also be calculated by baseline pathogen and its MIC categories. Safety summaries and analyses described in 6.6.1 will be performed without summaries of TEAEs up to the EOT, TEAEs leading to study discontinuation, SAEs and AEs of special interest, and listings.

For sepsis patients subset and sepsis evaluable patients subset described in section 4, demographic characteristics, patient characteristics, and disease characteristics will be summarized.

Criteria for sepsis patients subset and sepsis evaluable patients subset will be listed for all enrolled patients.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic characteristics [age, age group (≥20 – 45, 46 – 64, 65 – 74, ≥75), sex, ethnicity, and race] will be summarized for the MITT and safety analysis sets, and will be listed for all enrolled patients.

Patient characteristics [height, weight, BMI, BMI category (<18.5, 18.5 - <25, 25-<30, ≥30, Missing)] will be summarized for the MITT and safety analysis sets, and will be listed for all enrolled patients.

Disease characteristics [APACHE II score, APACHE II (≤10, >10 - ≤30, >30, Missing), Heart rate, Prior systemic antibiotics use in the previous 3 days before enrollment including the day of enrollment, Estimated CrCl, Primary and secondary diagnosis, Infection type (monomicrobial or polymicrobial), Study qualifying procedure] will be summarized for the MITT and safety analysis sets, and will be listed for all enrolled patients.

Imaging test will be listed for all enrolled patients.

The number of patients/pathogens with monomicrobial and polymicrobial infections will be summarized for the mMITT and eME at TOC analysis sets.

The number of pathogens identified at baseline will be summarized for the mMITT and eME at TOC analysis sets.

CAZ-AVI minimum inhibitory concentration (MIC) by baseline pathogen will be summarized for the mMITT and eME at TOC analysis sets.

Ceftazidime minimum inhibitory concentration (MIC) by baseline pathogen will be summarized for the mMITT and eME at TOC analysis sets.

The number of CAZ-AVI minimum inhibitory concentration (MIC) categories of baseline pathogens will be summarized for the mMITTand eME at TOC analysis sets.

The number of Ceftazidime minimum inhibitory concentration (MIC) categories of baseline pathogens will be summarized for the mMITT and eME at TOC analysis sets.

Minimum inhibitory concentration (MIC) for CAZ-AVI and other drugs will be summarized for pathogens isolated in this study, if available.

Medical history, current medical conditions, surgical history will be summarized for the MITT analysis set, and listed for all enrolled patients.

6.5.2. Study Conduct and Participant Disposition

Patients who enrolled, who received treatment, who did not receive the treatment, who completed treatment, who discontinued the treatment including the reason for discontinuation, who completed the study up to the TOC visit, and up to the LFU visit, who did not complete the study with the reason for discontinuation from the study, will be summarized and listed.

Important protocol deviations will be summarized and listed.

Patients in each of the analysis sets will be summarized and listed for all enrolled patients.

6.5.3. Study Treatment Exposure

Duration of exposure will be summarized for the safety, MITT, and CE at TOC analysis sets.

Study treatment compliance will be summarized for the safety, MITT, and CE at TOC analysis set and will be listed for the safety analysis set. Treatment compliance (%) over the entire treatment period is defined as the total number of infusions received divided by the total number of infusions expected, and then multiplied by 100. The expected number of infusions are adjusted for renal function at baseline and investigator adjustment decision post-baseline.

Administaration schedule will be listed for all enrolled patients.

6.5.4. Concomitant Medications and Nondrug Treatments

Prior systemic antibiotic medications will be summarized for the MITT analysis set, and will be listed for all enrolled patients.

Prior medications other than prior systemic antibiotic medications will be summarized for the MITT analysis set, and will be listed for all enrolled patients.Concomitant antibiotic medications will be summarized for the MITT analysis set, and will be listed for all enrolled patients.

Concomitant medications other than antibiotics will be summarized for the MITT analysis set, and will be listed for all enrolled patients.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Adverse events will be summarised in accordance with sponsor reporting standards using the safety analysis set. Only treatment emergent adverse events (TEAEs) will be summarized. However, all AEs will be presented in data listings.

All TEAEs during the study will be summarized by relationship to study drug (all causalities and treatment related) according to the MedDRA SOC and PT. TEAEs by severity and leading to study discontinuation will also be summarized, as well as SAEs. TEAEs summarized by overall and by SOC and PT will be aggregated by study period (up to the EOT visit and up to the LFU visit).

Listings will be presented by subject for all AEs as well as for SAEs, AEs associated with death, and AEs leading to discontinuation of the study drug.

Adverse events of special interest (Liver Disorders, Diarrhea, Hypersensitivity / Anaphylaxis, Hematological Disorders, Renal Disorders) will be summarized. The same definition as the global CTD will be used for adverse events of special interest (Appendix 2.7.4.7.1, Table 4.1.1.7.6 Adverse events of special interest - preferred term search strategies by safety topic and subgroup). However, the term will be used after the harmonization to the latest version of MedDRA. Event terms for adverse events of special interest will be listed.

Medication errors will be listed.

6.6.2. Laboratory Data

Laboratory data will be summarized and listed in accordance with the sponsor reporting standards using the safety population.

Hy's Law values will be listed for the safety population.

6.6.3. Vital Signs

Vital sign variables, weight, and BMI will be summarized by scheduled assessment including change from baseline for the safety analysis set. Box and whisker plots will be produced for the parameters (vital sign variables) [y-axis] against visit [x-axis]. Vital sign variables, weight, and BMI will be listed for the safety population.

6.6.4. Electrocardiograms

See section 6.5.1 (Heart rate evaluated either in the 12-lead ECG or in the monitor ECG will be measured at Screening).

Electrocardiogram data will be listed for the safety population.

6.6.5. Physical Examination

Not Applicable

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is an open label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment.

7.2. Interim Analyses and Summaries

Not Applicable.

8. REFERENCES

1. CLSI M100: Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition. Clinical and Laboratory Standards Institute. February 2022.

2. Guideline for Clinical Evaluation of Antibacterial Drugs. PSEHB/PED Notification No. 1023-3. October 23, 2017.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Visit	Analysis Type	Population
Clinical response	EOT, TOC, and LFU	Summary	MITT, mMITT, CE (CE at EOT, CE at TOC, and CE at LFU), ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU)
Per-patient microbiological response	EOT, TOC, and LFU	Summary	mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU)
Per-pathogen microbiological response	EOT, TOC, and LFU	Summary	mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU)
Per-pathogen microbiological response by MIC categories	EOT, TOC, and LFU	Summary	mMITT, ME (ME at EOT, ME at TOC, and ME at LFU), and eME (eME at EOT, eME at TOC, and eME at LFU)
Clinical response, Per-patient/Per-pathogen microbiological response, and Per-pathogen microbiological response by MIC categories	EOT, TOC, and LFU	Summary	Sepsis patients subset, and Sepsis evaluable patients subset
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Appendix 2. Data Derivation Details

Appendix 2.1. Definitions of Clinical Response at the EOT, TOC, LFU, and Early Termination/Discontinuation Visits

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antimicrobial therapy, drainage, or surgical intervention is necessary. Note: Patients who receive coverage for MRSA or Enterococcus, as allowed per protocol, can still have a response definition of cure.
Failure	Patients who meet any 1 of the criteria below will be considered a treatment failure: • Death related to intra-abdominal infection • Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or nonroutine wound care • Patient who receives treatment with additional antibiotics for ongoing symptoms of intra-abdominal infection (including patients prematurely discontinued from study drug due to an AE who require additional antibiotics for cIAI) • Patient previously met criteria for failure
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made • Death where cIAI is clearly noncontributory • Circumstances that preclude classification as a cure or failure

Appendix 2.2. Microbiological Response Categories at Day 1 (Baseline), EOT, TOC, LFU, and Early Termination/Discontinuation Visits

Microbiological response	Definition
Eradication	Absence of causative pathogen from appropriately obtained specimens at the site of infection.
Presumed eradication	Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.
Colonization	Obvious symptoms and signs of the infection have resolved in response to the treatment, but the initial causative bacteria are detected at the same site.
Persistence	Causative organism still present at or beyond the EOT visit from a culture of intra-abdominal abscess, peritonitis, or surgical wound infection.
Persistence with increasing MIC	Continued presence of the causative organism in a culture of the intra-abdominal abscess, peritonitis, or surgical wound infection obtained during or upon completion of treatment with IV study intervention, and the pathogen that was susceptible to IV study intervention pre-treatment displays a ≥4-fold higher MIC to IV study intervention after treatment with IV study intervention.
Presumed persistence	Patient was previously assessed as a clinical failure and repeat cultures were not performed/clinically indicated.

Microbiological response	Definition
Indeterminate microbiological response	Study data are not available for evaluation of efficacy, for any reason including: • Patient lost to follow-up such that a determination of microbiological response cannot be made • Death where cIAI is clearly noncontributory • Circumstances that preclude classification as eradication, presumed eradication, colonization, persistence, persistence with increasing MIC, and presumed persistence • Patient with no pathogen isolated from a cIAI culture obtained at Baseline or for whom a culture was not obtained.

Appendix 2.3. Emergent Infections

Emergent Infection	Definition
Superinfection	Emergence of new pathogen during treatment with IV study intervention, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Emergence of new pathogen after completion of treatment with IV study intervention, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
APACHE II	acute physiology and chronic health evaluation II
AST	aspartate aminotransferase
AVI	avibactam
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CAZ	ceftazidime
CE	clinically evaluable
CI	confidence interval
cIAI	complicated intra-abdominal infection
CLSI	Clinical & Laboratory Standards Institute
CrCL	creatinine clearance
CV	coefficient of variation
ECG	electrocardiogram
EOT	end of treatment
ESBL	extended spectrum beta lactamase
eME	extended-microbiologically evaluable
FSH	follicle-stimulating hormone
GGT	gamma-glutamyltransferase

Abbreviation	Term
IV	intravenous
LFU	late follow-up
LLOQ	lower limit of quantitation
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
MTZ	metronidazole
PK	pharmacokinetic(s)
qSOFA	quick Sequential Organ Failure Assessment
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOFA	Sequential Organ Failure Assessment
TBili	total bilirubin
TOC	test of cure
WBC	white blood cell