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

Study Intervention Number:	PF-06947386
Study Intervention Name:	Ceftazidime-Avibactam
US IND Number:	Not applicable (N/A)
EudraCT Number:	N/A
Protocol Number:	C3591036
Phase:	3

Short Title: A Phase 3 Study to Assess Efficacy and Safety of PF-06947386 in Japanese Adult Participants With Complicated Intra-abdominal Infections

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	21 July 2021	Summary and rationale for changes are shown below with revised language shown as underlined text. Section 1.1 Number of Participants, Section 4.1, Section 9.2: • Following Pharmaceuticals and Medical Devices Agency (PMDA) feedback, added language about the anticipated number of enrolled participants who meet the definition of sepsis patients subset. Although it is uncertain whether the definition of the sepsis patients subset (Section 9.3) is met at the timing of study entry, 3 to 5 enrolled participants are anticipated to meet the definition of the sepsis patients subset. Section 1.3 Schedule of Activities, Section 8.1.7.2: • Clarified the explanation about initial qualifying procedure. Original language: initial qualifying procedure (performed within 24 hours of entry) Revised language: initial qualifying procedure [performed within 24 hours of entry for preoperative enrollment (see Section 5.1, inclusion criterion 3)] Section 5.2 Exclusion Criterion 21: • Clarifications were made in the text about using concomitant systemic antibacterials or systemic antifungals. Original language: Participant needs effective concomitant systemic antibacterials (oral, IV, or intramuscular) or systemic antifungals in addition to that designated in the study group, except vancomycin, linezolid, or daptomycin if started for known or suspected

		MRSA or *Enterococcus* species as per protocol Section 6.5 Revised language: Participant needs effective concomitant systemic antibacterials (eg, oral, IV, or intramuscular) or systemic antifungals in addition to study regimens, except vancomycin, linezolid, or daptomycin if started for known or suspected MRSA or *Enterococcus* species as per protocol Section 6.5 Section 6.1.1.2, Table 6 footnote: • Added language describing the impact of initiating hemodialysis during the treatment period. PF-06947386 and metronidazole are removed by hemodialysis. Dosing of PF-06947386 and metronidazole on hemodialysis days should occur after completion of hemodialysis. In cases where hemodialysis is needed but scheduling the dosing of PF-06947386 and metronidazole after completion of hemodialysis is not feasible, or if the investigator has concerns for the participant to continue with dosing, discontinuation from study treatment may be considered, as needed. Section 6.3.1: • As cIAI patients require immediate medical attention, modifications were made to enable the start of study regimens when eligibility of the study participant is confirmed by the investigator or designee, as clarified in PACL dated 22 June 2021. Original language: Registration will be performed centrally by the sponsor or designee for all participants. Following full assessment and determination that the participant meets all eligibility criteria, the investigator or designee will fax or email a complete the registration form to the sponsor or designee. The sponsor or designee will assign a participant identification number, which will be

		used on all CRF pages and other trial-related documentation or correspondence referencing that participant and fax or email to the site. No participant shall receive IP until the investigator or designee has received the above information from the sponsor or designee: confirmation of the participant's enrollment. Revised language: Following full assessment and determination that the participant meets all eligibility criteria, the investigator or designee may administer IP to the participant. The investigator or designee will fax or email a completed registration form to the sponsor. The investigator or designee shall receive the enrollment number from the sponsor via fax or email. Section 6.5: • Clarifications were made in the text describing the use of antifungals and added language shown in underlined text below. Topical antibacterial and topical antifungals are permitted except that they may not be applied to the surgical site. It is anticipated that in instances of clinical failure, alternative "rescue" antibacterial therapy to treat the cIAI would be instituted. Systemic antifungal therapy should be avoided unless clinically indicated. Section 8.1.3: • Added "abdominal pain" to the definition of abdominal signs and symptoms, as clarified in PACL dated 22 June 2021. Original language: Abdominal signs and symptoms will be defined as nausea, vomiting, tenderness to palpation, rebound tenderness, guarding, mass, ascites, chills. Revised language:

		Abdominal signs and symptoms will be defined as abdominal pain, nausea, vomiting, tenderness to palpation, rebound tenderness, guarding, mass, ascites, chills. Section 9.4.2: • For ensuring consistency in this document, added "MITT" to the analysis sets on which supplemental analyses for the primary endpoint will be performed as shown in underlined text below. Supplemental analyses will be performed on the MITT, mMITT, ME, and eME analysis sets. Section 10.4.4: • The following modifications were made as there are no available female condoms and spermicides that are currently approved in Japan, as clarified in PACL dated 22 June 2021. Original language: Male or female condom with or without spermicide. * Not approved in Japan Revised language: Male or female* condom with or without spermicide*. * Not approved in Japan In addition, minor typographical/editorial errors were corrected throughout the document.
Original protocol	19 April 2021	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 3 Study to Assess Efficacy and Safety of PF-06947386 in Japanese Adult Participants With Complicated Intra-abdominal Infections

Rationale

Ceftazidime is an injectable third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years for the treatment of infections caused by aerobic Gram-negative pathogens. Ceftazidime has been shown to be safe and effective in adult and pediatric patients for a range of indications. However, over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of resistance is bacterial production of β-lactamases, in particular, ESBLs. In order to counter ceftazidime resistance and restore antibacterial activity to ceftazidime, a combination product has been developed in which ceftazidime is combined with avibactam, a novel non-β-lactam β-lactamase inhibitor.

PF-06947386 has received regulatory approval in 78 countries/regions as of August 2020 including approval in the US in February 2015 and in the EU in June 2016. PF-06947386 is indicated in the US and Europe for the treatment of adults with cIAI, cUTI and HAP/VAP. In Europe, it is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options and, in 2020, it was approved for the treatment of bacteremia associated with, or suspected to be associated with, any of the above infections.

The PK of ceftazidime and avibactam is sufficiently similar across indications, and in Japanese, non-Japanese and non-Asian patient populations, therefore, dose adjustment based on race is not required. Population PK modeling/simulation analysis has demonstrated sufficient exposure and high PTA in Japanese patients at the adult doses currently approved outside of Japan.

There are no notable differences in diagnostics and treatment for cIAI between Japan and overseas. These infections require operative intervention or percutaneous drainage in conjunction with broad spectrum antibacterial therapy. Almost all intra-abdominal infections are polymicrobial and are caused by organisms from the gastrointestinal tract, including aerobes and facultative and obligate anaerobes. Gram-negative *Enterobacterales* are most commonly isolated. Currently, ESBLs producing pathogens are increasing among the *Enterobacterales,* such as *Escherichia coli.*

For the treatment of cIAI, broad-spectrum single agent (β-lactam/β-lactamase inhibitor combination drugs, carbapenem) or combination therapy regimens (concomitant use of cephem antibiotics) are recommended[*].

The *in vitro* activity of ceftazidime-avibactam and comparator antibiotics was determined against year 2017 clinical isolates using the broth microdilution methodology recommended by CLSI. A total of 6046 isolates were obtained from hospitalized patients in 23 medical centers within 6 countries (Australia, Japan, South Korea, Philippines, Taiwan, and Thailand) from the Asia Pacific region in 2017. Ceftazidime-avibactam had potent activity against the majority of clinical isolates studied, in particular against Gram-negative organisms for the target pathogens in the package insert. The MIC of domestic clinical isolates in 2017 was the same as that of clinical isolates in overseas.

The efficacy and safety of PF-06947386 have been demonstrated in patients with cIAI, cUTI and HAP/VAP in confirmatory global studies. Japanese patients were included in studies in patients with cUTI and HAP/VAP.

Based on the above, PF-06947386 is expected to be efficacious in Japanese patients with cIAI and no new safety issues have been identified in Japanese patients when avibactam is added to ceftazidime at the same dose used in the global studies. In addition, this drug is considered to contribute to the treatment of AMR.

Objectives, Estimands, and Endpoints

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 Table 7. 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	• Clinical response at the TOC visit

[*] Takesue Y. Antibiotic selection and duration of administration in patients with intra-abdominal infections according to the grade of severity: In comparison with the Surgical Infection Society revised guidelines of the management of intra-abdominal infection. Journal of Japan Society for Surgical Infection 2019;16(2):80-6.

Objectives	Estimands	Endpoints
	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 Table 7. 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 Table 7. 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-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Table 7. All data after intercurrent events of receiving insufficient amount of study drug or any protocol deviations that affect assessment of efficacy will not be	

Objectives	Estimands	Endpoints
	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 Table 7. 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 Table 8. Proportion of participants with favorable microbiological response will be calculated. • Estimand 12: the estimand of the secondary endpoints The trial will estimate the average treatment effect of PF-06947386 plus metronidazole in	• Clinical response at EOT, and LFU visits • Per-patient microbiological response at EOT, TOC, and LFU visits

Objectives	Estimands	Endpoints
	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 Table 8. 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 Table 8. 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 the treatment of patients with cIAIs	N/A	• AEs and SAEs, all cause mortality, reasons for discontinuations of IV study intervention and study, vital sign measurements, and potentially clinically

Objectives	Estimands	Endpoints
		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]

Overall Design

Study C3591036 will assess the efficacy and safety of PF-06947386 in Japanese patients with cIAI requiring hospitalization. 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.

Number of Participants

Approximately 60 participants will be enrolled to study intervention such that there will be approximately 50 evaluable participants in the CE analysis set. Although it is uncertain whether the definition of the sepsis patients subset (Section 9.3) is met at the timing of study

entry, 3 to 5 enrolled participants are anticipated to meet the definition of the sepsis patients subset.

Note: "Enrolled" means a participant's, or his or her legally authorized representative'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.

Intervention Groups and Duration

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. 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.

Data Monitoring Committee or Other Independent Oversight Committee: Yes

This study will use an adjudication committee. The adjudication committee is independent of the study team and includes only external members. The adjudication committee will consist of 2 or more external infectious disease specialists especially intra-abdominal infection. The adjudication committee charter describes the role of the adjudication committee in more detail. The adjudication committee will review investigators' assessments, including clinical response, based on the collected data for consistency of evaluation in the study. If a discrepancy exists between the adjudication committee and investigators, the assessment by the adjudication committee will prevail. For details, see Section 8.1.6.1.

Statistical Methods

The primary endpoint for the study is clinical response at the TOC visit. The proportion and the 95% CI will be calculated. The primary analysis will be performed on the CE analysis set.

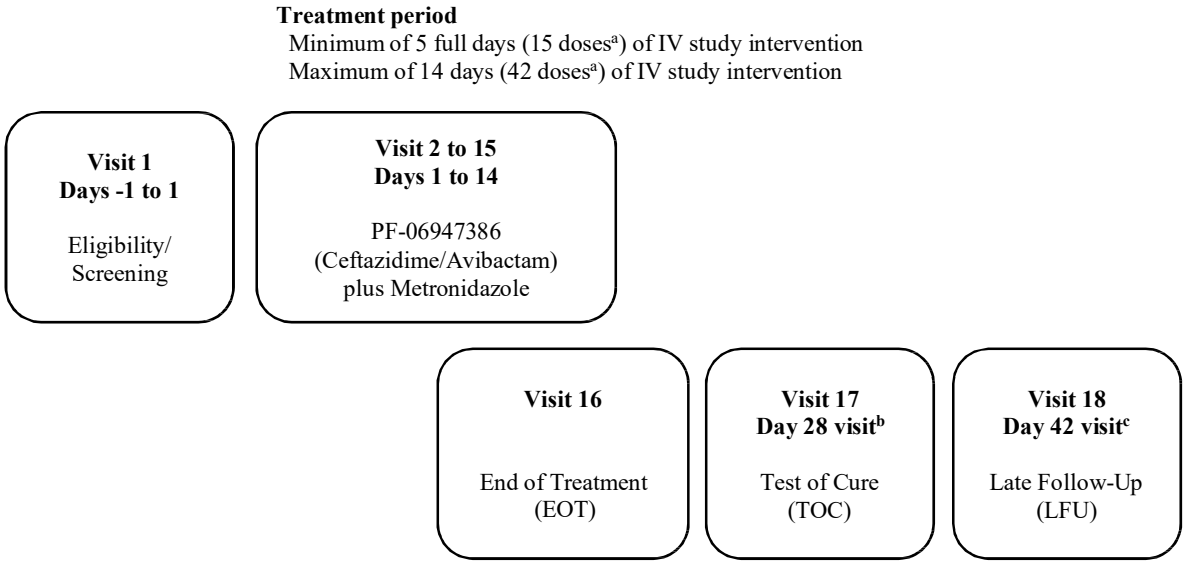
In this study, no formal hypothesis testing will be conducted.

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%.

Safety endpoints such as AEs, laboratory test results, and vital sign measurements will be summarized and evaluated descriptively.

1.2. Schema

Figure 1. Study Outline



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

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Activity	**Screening**	**Baseline/ first IV Infusion[a]**	**Treatment**	**End of Treatment**	**Test of Cure[e]**	**Late Follow-Up[f]**	**Early Termination/ Discontinuation[b]**
Visit Number	**Visit 1**	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**	
Study Day	**Days -1 to 1**	**Day 1[c]**	**Days 2 to 14[c]**	**within 24 hrs after completion of last IV infusion**	**Day 28 visit (Day 28-35)**	**Day 42 visit (Day 42-49)**	
Study Procedures							
Informed consent	X						
Inclusion/Exclusion criteria	X	X					
APACHE II score[d]	X						
Demographics	X						
Medical and surgical history	X						
Clinical/Safety Assessments							
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulse rate, blood pressure, respiratory rate[j]	X	X	Daily	X	X	X	X
Heart rate[k]	X						
Height/weight	X[l]	Repeat weight only to calculate CrCL when clinically indicated.					
Imaging test[m]	When available						

Protocol Activity	Screening	Baseline/ first IV Infusion[a]	Treatment	End of Treatment	Test of Cure[e]	Late Follow-Up[f]	Early Termination/ Discontinuation[b]
Visit Number	**Visit 1**	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**	
Study Day	**Days -1 to 1**	**Day 1[c]**	**Days 2 to 14[c]**	**within 24 hrs after completion of last IV infusion**	**Day 28 visit (Day 28-35)**	**Day 42 visit (Day 42-49)**	
Description of operative procedure	From initial qualifying procedure [performed within 24 hours of entry for preoperative enrollment (see Section 5.1, inclusion criterion 3)] and any additional procedures performed during the study period.						
Clinical response assessment[n]				X	X	X	X
Microbiological response assessment[n]				X	X	X	X
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X
Investigator case summary/operative notes/discharge summary[o]	When available						
Laboratory assessments							
Estimated CrCL[p]	X	X[h]	As clinically indicated: use local serum creatinine measurements				
Blood and urine for safety[q]	X	X	Day 2, and every 3 days thereafter while on IV therapy	X	X	X	X
β-hCG[r]	X				X	X	X
Contraception check	X	X		X	X	X	X
Study Medication							
Study drug infusion (PF-06947386, metronidazole)[s]		X	X[a, c]				
PK blood sampling[t]			X				

Protocol Activity	Screening	Baseline/ first IV Infusion[a]	Treatment	End of Treatment	Test of Cure[e]	Late Follow-Up[f]	Early Termination/ Discontinuation[b]
Visit Number	**Visit 1**	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**	
Study Day	**Days -1 to 1**	**Day 1[c]**	**Days 2 to 14[c]**	**within 24 hrs after completion of last IV infusion**	**Day 28 visit (Day 28-35)**	**Day 42 visit (Day 42-49)**	
Prior and concomitant treatment/antibiotics	X	X	Daily	X	X	X	X
Microbiology							
Blood culture[u]	X		Day 2, and every 3 days thereafter while on IV therapy	X	X	X	X
Culture of abdominal infection site[u]	Cultures must be obtained at initial qualifying procedure [performed within 24 hours of entry for preoperative enrollment (see Section 5.1, inclusion criterion 3)]. If additional procedures are performed, additional abdominal site cultures should be obtained. Cultures from the wound/procedure site should be obtained only if clinically indicated through study end.						

Abbreviations: β-hCG, beta-human chorionic gonadotropin; cIAI, complicated intra-abdominal infection; CrCL, creatinine clearance; EOT, End of Treatment; IV, intravenous; LFU, Late Follow-Up; PK, pharmacokinetic(s); TOC, Test of Cure.

a. The first dose of IV study intervention is given at Visit 2 on Study Day 1. All assessments during Visit 2 must occur prior to first dose of IV study intervention.

b. If a participant terminates early from study drug treatment or discontinues from participation in the study, procedures for "Early Termination/ Discontinuation" will be conducted. In addition, if possible, any AEs that occur prior to use of other treatments for cIAI and pregnancy must be reported for a minimum of approximately 28 days after the last administration of the study drug up to study end. These contacts may occur via telephone, postal mail, or other means of communication with the participant.

c. Study Day 1 is the day of the first administration of study intervention. Participants will receive a minimum of 5 full days (15 doses) of IV study intervention up to a maximum of 14 days (42 doses) of study intervention. Dosing may occur on Day 15 depending on the time of day when the first dose of IV study intervention is given on Study Day 1.

d. Calculate APACHE II score using most recent local laboratory results. Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. See Section 10.6. If ABG is not clinically indicated, the APACHE II score should be calculated using serum bicarbonate and oxygenation should be presumed normal.

e. For example, if a patient is enrolled on the first day of the month, the TOC visit should be performed on the 28th day of the month. If it is not possible to perform the TOC visit after 28 calendar days from the day of the first IV infusion, the allowed visit window is 28 to 35 calendar days after the day of the first IV infusion.

f. If it is not possible to perform the LFU visit after 42 calendar days from the day of the first IV infusion, the allowed visit window is 42 to 49 calendar days from the day of the first IV infusion.

g. Surgical wound examination should occur daily even if inspection is limited by the presence of surgical dressing (within the first 24 to 48 hours after surgery) or the presence of a negative pressure wound therapy device. A full examination of the wound unimpeded by the surgical dressing should occur starting approximately 24 to 48 hours after surgery or earlier if the surgeon feels it is safe to remove the dressing. For patients with negative pressure wound therapy devices, a thorough wound evaluation should occur when a full dressing change is performed.

h. Assessment is only required at Visit 2 if Visit 1 and Visit 2 occur on different days or are separated by surgery.

c [redacted]

j. Assess pulse rate and blood pressure after patient is resting in supine position for at least 5 minutes (see Section 8.2.3).

k. Heart rate may be evaluated either in the 12-lead electrocardiogram or in the monitor electrocardiogram.

l. Recently measured height and weight results may be used if patient is not ambulatory at the time of Screening.

m. Imaging tests are not required for the study, but the results should be submitted if done as part of the diagnosis. Imaging tests include plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

n. If a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

o. All required documentation including surgical reports and imaging results may be submitted if requested by the Adjudication Committee. See Section 8.1.6.1 for information regarding the Adjudication Committee.

p. Calculate estimated CrCL using Cockcroft-Gault formula (See Section 10.8). For details regarding dosing in renal impairment see Section 6.1.1.

q. Safety labs should be collected at Screening, Baseline (only if surgery occurs between Screening and Baseline visits or if >12 hours has passed between Screening and Baseline visit), every 3 days while on IV therapy (Day 2, Day 5, Day 8, etc.), EOT, TOC, LFU, and Early Termination/Discontinuation visits. See Section 8.2.5.

r. 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.

s. If necessary, a 1-time dosing interval adjustment is allowed after the first dose of IV study intervention to create a suitable dosing schedule going forward with an 8-hours (±30 minutes) dosing interval. The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a 1-time 4-hour dosing interval is allowed between the first and the second dose). If a 1-time dosing interval adjustment is implemented for the second dose, all further dosing times will be calculated based on the time of the second dose.

t. Blood samples for PK will be collected on either Day 3 or Day 4, following a dose administration that is convenient for sample collections. Three samples will be collected at the following times: 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. All efforts will be made to obtain 3 samples, 1 from each of the 3 time windows, for each

participant. For example, 1) 10 minutes prior to stopping the first PF-06947386 infusion on Day 3, 2) 60 minutes after stopping the first PF-06947386 infusion on Day 4, 3) 5 hours after stopping the second PF-06947386 infusion on Day 3, etc. Blood for PK must NOT be drawn from the same arm used for IV drug administration. See Section 8.5.

u. If blood cultures are positive, the assessment is to be repeated at the scheduled time points. Blood cultures should also be performed as clinically indicated. For instructions on collection and processing of blood cultures and abdominal site cultures, see Section 8.1.7.

2. INTRODUCTION

PF-06947386 is currently being developed in hospitalized adult participants with cIAI in Japan.

2.1. Study Rationale

PF-06947386 is a combination drug that contains ceftazidime, the third generation cephalosporin antibiotic (β-lactam) and avibactam, a new β-lactamase inhibitor. The purpose of the study is to assess the efficacy and safety data in Japanese hospitalized patients with cIAI.

2.2. Background

2.2.1. Mechanism of Action/Indication

Ceftazidime is an injectable third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years for the treatment of infections caused by aerobic Gram-negative pathogens. Ceftazidime has been shown to be safe and effective in adult and pediatric patients for a range of indications. However, over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of resistance is bacterial production of β-lactamases, in particular, ESBLs. In order to counter ceftazidime resistance and restore antibacterial activity to ceftazidime, a combination product has been developed in which ceftazidime is combined with avibactam, a novel non-β-lactam β-lactamase inhibitor.

Ceftazidime has a wide antibacterial spectrum that includes Gram-positive bacteria and Gram-negative bacteria, and especially, it shows strong antibacterial mechanism against glucose non-fermenting Gram-negative bacilli due to its high outer-membrane permeability in Gram-negative rods. Ceftazidime shows antibacterial activity against Gram-negative pathogens such as *Escherichia coli, Citrobacter freundii, Klebsiella oxytoca, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Morganella morganii, Providencia* spp.*, Haemophilus influenzae, Pseudomonas aeruginosa*.

Avibactam inhibits the class A β-lactamase enzymes including ESBLs and *Klebsiella pneumoniae* carbapenemase-type β-lactamases (KPCs), and unlike previous β-lactamase-inhibitors, avibactam also inhibits class C β-lactamases such as the chromosomally-encoded AmpC enzymes (AmpC type cephalosporinase) found in *Enterobacterales* and *P. aeruginosa* and plasmid-encoded class C β-lactamases, for example CMY-2; and some of the class D β-lactamases (eg OXA-48 type carbapenemase). However, it does not inhibit class B metallo-β-lactamases.

Avibactam binds to class A enzymes with a lower inhibition IC_{50} as compared to currently marketed β-lactamase inhibitors, ie clavulanic acid, tazobactam and sulbactam. In addition, avibactam is a potent inhibitor of class C enzymes whereas clavulanic acid, tazobactam and sulbactam lack any clinically useful activity. Also, avibactam does not induce class C β-lactamase production.

A fixed dose combination of ceftazidime-avibactam was approved for use in adults by the FDA in February 2015, and in children aged 3 months and older (cIAI in combination with metronidazole, or cUTI) in March 2019 and is marketed under the tradename Avycaz[1]. In June 2016, the European Commission granted European Union marketing authorization for the use of PF-06947386 in adults under the tradename Zavicefta®[2]. Currently, ceftazidime-avibactam was also approved for pediatric use in the EU.

PF-06947386 has received regulatory approval in 78 countries/regions as of August 2020. PF-06947386 is indicated in the US and Europe for the treatment of adults with cIAI, cUTI, and HAP, including VAP. In Europe, it is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options and, in 2020, it was approved for the treatment of bacteremia associated with, or suspected to be associated with, any of the above infections.

2.2.2. Development of PF-06947386 in Japan

In Japan, PF-06947386 was co-developed by AstraZeneca and Forest Research Institute for the treatment of cUTI, cIAI and HAP including VAP. This drug was approved in February 2015 in the US and in June 2016 in the EU. Thereafter, in August 2016, Pfizer took on the responsibility for development and commercialization in countries except the United States and Canada. AstraZeneca conducted the multi-regional Phase 3 studies (RECAPTURE for cUTI, REPROVE for HAP/VAP) which included Japanese patients. Participation from Japan was continued until 2014. Pfizer decided to take on the responsibility to develop this drug in Japan with consideration that AMR is one of the important issues in Japan. It is considered highly necessary to develop new drugs that are effective for resistant bacteria, and this drug is considered to contribute to the treatment of AMR.

2.2.3. Rationale for Conducting This Study

As shown in Section 2.2.4.1, the PK of ceftazidime and avibactam was sufficiently similar across indications, and in Japanese, non-Japanese and non-Asian participants, therefore, dose adjustment based on race is not required. Population PK modeling/simulation analysis has demonstrated sufficient exposure and high PTA in Japanese patients at the adult doses currently approved outside of Japan.

There are no notable differences in diagnostics or treatment for cIAI between Japan and overseas. These infections require operative intervention or percutaneous drainage in conjunction with broad spectrum antibacterial therapy. Almost all intra-abdominal infections are polymicrobial and are caused by organisms from the gastrointestinal tract, including aerobes and facultative and obligate anaerobes. Gram-negative *Enterobacterales* are isolated most commonly[3]. Currently, ESBL producing pathogens are increasing in the *Enterobacterales* such as *Escherichia coli*[4].

For the treatment of cIAI, broad-spectrum single agent (β-lactam/β-lactamase inhibitor combination drugs, carbapenem) or combination therapy regimens (concomitant use of cephem antibiotics) are recommended[4].

The *in vitro* activity of ceftazidime-avibactam and comparator antibiotics was determined against year 2017 clinical isolates using the broth microdilution methodology recommended by CLSI. A total of 6046 isolates were obtained from hospitalized patients in 23 medical centers within 6 countries (Australia, Japan, South Korea, Philippines, Taiwan, and Thailand) from the Asia Pacific region in 2017. Ceftazidime-avibactam had potent activity against the majority of clinical isolates studied, in particular against Gram-negative organisms for the target pathogens in the package insert. The MIC of domestic clinical isolates in 2017 was the same as that of clinical isolates in overseas.

As shown in Section 2.2.4.2, the efficacy and safety of PF-06947386 have been demonstrated in patients with cIAI, cUTI and HAP/VAP in confirmatory global studies. Japanese patients were included in studies in patients with cUTI and HAP/VAP.

Based on the above, PF-06947386 is expected to be efficacious in Japanese patients with cIAI and no new safety issues have been identified in Japanese patients when avibactam is added to ceftazidime at the same dose used in the global studies. In addition, this drug is considered to contribute to the treatment of AMR.

2.2.4. Clinical Overview

Brief descriptions of completed clinical studies are provided below from the viewpoints of PK/PD in Section 2.2.4.1 and results of clinical studies in patients with cIAI in Section 2.2.4.2.

2.2.4.1. Pharmacokinetics/Pharmacodynamics in Japanese, Chinese and Non-Asian Populations

The activity of ceftazidime and avibactam is directly on the infecting bacteria, so the mechanism of action and the PK/PD target is assumed to be the same regardless of race. It was demonstrated that the *in vitro* activity of ceftazidime-avibactam against isolates from Japanese patients is similar to non-Asian populations, providing evidence that microbiological etiology is comparable. Therefore, PK data can be used to extrapolate clinical efficacy from non-Japanese populations to Japanese patients. Like other β-lactam antibiotics, ceftazidime-avibactam was found to be a drug with low ethnic sensitivity. The effect of race on PK of ceftazidime and avibactam has been assessed, as described below, and it was concluded that dose adjustment by race is not required.

The steady state PK parameters of ceftazidime and avibactam in healthy Japanese, Chinese and non-Asian participants are listed in Table 1. The mean exposure of ceftazidime was slightly higher in Japanese (29% $C_{ss,max}$ and 13% AUC_{ss}) and Chinese (27% $C_{ss,max}$ and 4% AUC_{ss}) compared with non-Asian. Also the mean exposure of avibactam was slightly higher in Japanese (5% $C_{ss,max}$ and 8% AUC_{ss}) and Chinese (23% $C_{ss,max}$ and 11% AUC_{ss}) compared with non-Asian; however, the observed differences in PK between these studies are modest, so dose adjustments based on race are not considered warranted.

Table 1. PK Parameters of Ceftazidime and Avibactam (Geometric Mean [CV%]) for 2.0 g Ceftazidime + 0.5 g Avibactam 2 Hour IV Infusion q8h in Japanese (Study D4280C00010), Chinese (Study D4280C00020), and Non-Asian Participants (Study D4280C00011 Part A)

PK parameters	Japanese participants (N=7)	Non-Asian participants (N=12)	Chinese participants (N=12)
Ceftazidime			
$C_{ss,max}$ (µg/mL)	113.1 (15.3)	87.7 (16.7)	111.1 (14.6)
AUC_{ss} (µg.h/mL)	348.2 (17.2)	308.2 (15.8)	321.5 (15.5)
Avibactam			
$C_{ss,max}$ (µg/mL)	15.0 (20.6)	14.3 (19.1)	17.6 (18.1)
AUC_{ss} (µg.h/mL)	42.2 (14.4)	39.2 (21.7)	43.6 (19.1)

Source: Study D4280C00010 CSR Errata list and Addendum, Study D4280C00011 CSR, and Study D4280C00020 CSR

Furthermore, the potential impact of race on ceftazidime and avibactam PK in patients was explored using the final population PK model for PF-06947386 (CAZ-MS-09). Similar results were observed for Japanese vs non-Asian patients as those of healthy participants. In the final model, Japanese race was not identified as a key covariate in the ceftazidime or avibactam population PK models. Predicted ceftazidime and avibactam exposures at steady state ($C_{ss,max}$ and $AUC_{ss,24}$), and rates of attainment for the joint target [ie, 50% *f*T>MIC (percentage of time over the 50% dosing interval that free ceftazidime concentrations exceed MIC) for ceftazidime and 50% *f*T>1.0 mg/L (percentage of time over the 50% dosing interval that free avibactam concentrations exceed the threshold concentration) for avibactam], were calculated for each race subgroup from the Phase 3 cUTI, cIAI, and HAP/VAP studies using the population PK model-estimated post-hoc PK parameters. Mean predicted exposures were slightly higher in the 45 Japanese patients (13 patients with HAP/VAP from REPROVE; 32 patients with cIAI from RECAPTURE) compared to the Caucasian/Other group (total 1209 patients with cUTI, cIAI, and HAP/VAP), with Japanese having approximately 32% higher $C_{ss,max}$ and 20% higher $AUC_{ss,24}$ for ceftazidime and approximately 34% higher $C_{ss,max}$ and 21% higher $AUC_{ss,24}$ for avibactam compared with Caucasian/Other. This slightly higher exposure resulted in 100% target attainment in Japanese patients (Table 2).

Table 2. Comparison of Ceftazidime and Avibactam Exposure and Target Attainment in Phase 3 Patients Stratified Across Different Races

Covariate Category:	N	CAZ $C_{ss,max}$ (µg/mL)	CAZ $AUC_{ss,24}$ (µg.h/mL)	AVI $C_{ss,max}$ (µg/mL)	AVI $AUC_{ss,24}$ (µg.h/mL)	Target attainment (%) (95%CI)
Race						
Caucasian/ Other	1209	68.6 (112.9)	848 (125.0)	12 (159.4)	135 (161.3)	98.3 (97.6, 99.1)

Table 2. Comparison of Ceftazidime and Avibactam Exposure and Target Attainment in Phase 3 Patients Stratified Across Different Races

Covariate Category:	N	CAZ $C_{ss,max}$ (µg/mL)	CAZ $AUC_{ss,24}$ (µg.h/mL)	AVI $C_{ss,max}$ (µg/mL)	AVI $AUC_{ss,24}$ (µg.h/mL)	Target attainment (%) (95%CI)
Race						
Asian non-Chinese/ non-Taiwanese/ non-Japanese	248	82.2 (118.4)	968 (121.9)	14.9 (166.5)	166 (170.8)	99.6 (98.8, 100.0)
Chinese & Taiwanese	262	77.6 (112.5)	884 (120.5)	14.7 (154.9)	151 (155.1)	98.9 (97.6, 100.0)
Japanese	45	90.4 (82.6)	1021 (94.8)	16.1 (134.3)	164 (130.9)	100.0 (N/A)

Note: Geometric mean (%CV) are reported for $C_{ss,max}$ and $AUC_{ss,24}$. Target attainment rates are reported as the observed percent (95% CI) of patients who achieved the joint target of 50% *f*T >PF-06947386 MIC of 8 mg/L for ceftazidime and 50% *f*T >1.0 mg/L for avibactam.
Source: CAZ-MS-09 Population Pharmacokinetic Report, Table 13

2.2.4.2. Results of Clinical Studies in Patients With cIAI

The results of overseas clinical studies in cIAI patients are provided below.

2.2.4.2.1. Clinical Efficacy in Studies for Complicated Intra-Abdominal Infections (RECLAIM, RECLAIM3)

The Phase 3 studies RECLAIM and RECLAIM3 were multinational, multicenter, randomized, double-blind comparative studies of PF-06947386 plus metronidazole with the exception of vancomycin, linezolid, or daptomycin which are used for the treatment of known or suspected MRSA or *Enterococcus* spp.

In RECLAIM, due to the difference between the guidelines issued by the FDA and EMA, two separate primary objectives and two separate SAPs were developed for US and for ROW, respectively. The RECLAIM protocol is aligned with the FDA SAP, whereas this protocol describes the analyses defined in the ROW SAP. In both RECLAIM and RECLAIM3, the primary endpoint was to assess the non-inferiority of PF-06947386 plus metronidazole compared to meropenem with respect to clinical cure at TOC (28 calendar days from randomization) visit. In both studies, non-inferiority was to be concluded if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) for the difference in the primary outcome variable between the treatment groups was greater than -12.5% for the primary outcome variable. In RECLAIM, the co-primary analysis sets were the MITT analysis set and patients who are CE at TOC; in RECLAIM3, the primary analyses set was the CE at TOC.

No Japanese patients were enrolled in either RECLAIM or RECLAIM3.

Result of primary analysis

The non-inferiority of PF-06947386 plus metronidazole compared to meropenem was demonstrated in relation to clinical response at the TOC visit in both RECLAIM and RECLAIM3 (Table 3). Clinical response at different time points (EOT, LFU) and analysis sets was broadly consistent with the conclusion of non-inferiority of PF-06947386 plus metronidazole compared to meropenem.

Table 3. Primary Analysis: Clinical Response at TOC: RECLAIM and RECLAIM3 (CE and MITT Analysis Sets)

Analysis set	Number (%) of patients		
Response	**PF-06947386 + MTZ**	**Meropenem**	**Difference[a] (%) 95% CI[b]**
RECLAIM			
MITT	N=520	N=523	
Clinical cure	429 (82.5)	444 (84.9)	-2.4 (-6.90, 2.10)
Clinical failure	47 (9.0)	39 (7.5)	
Indeterminate	44 (8.5)	40 (7.6)	
CE	N=410	N=416	
Clinical cure	376 (91.7)	385 (92.5)	-0.8 (-4.61, 2.89)
Clinical failure	34 (8.3)	31 (7.5)	
RECLAIM3			
CE	N=177	N=184	
Clinical cure	166 (93.8)	173 (94.0)	-0.2 (-5.53, 4.97)
Clinical failure	11 (6.2)	11 (6.0)	

a. Difference = difference in clinical cure rates (PF-06947386 + metronidazole treatment group minus meropenem treatment group).
b. The CI for the difference was calculated using the unstratified Miettinen and Nurminen method. Percentages were based on total number of patients in the treatment group (N).
Source: EU-CTD 2.5, Table 4

2.2.4.2.2. Clinical Efficacy by Causative Pathogen for Complicated Intra-Abdominal Infections: Pooled Phase 2/3 cIAI Studies

Across the pooled Phase 2/3 cIAI studies (RECLAIM, RECLAIM3, Study 2002, REPRISE-cIAI), PF-06947386 plus metronidazole demonstrated clinical efficacy (cure rate ≥70% and similar to comparator) against Gram-negative organisms that are amongst the most common causative pathogens in cIAI: *E. coli, K. pneumoniae, P. aeruginosa, K. oxytoca, C. freundii* and *E. cloacae* (Table 4).

Table 4. Clinical Response at TOC, by Common (Combined Frequency of ≥10) Baseline Gram-Negative Pathogen (Pooled Phase 2/3 cIAI Studies, mMITT Analysis Sets)

	Number of patients with cure / Total number of patients (%)	
Baseline pathogen	**PF-06947386 + MTZ (N=651)**	**Comparator (N=662)**
All	534/651 (83.2)	568/661 (85.9)
Enterobacterales	429/528 (81.3)	490/562 (87.2)
Citrobacter freundii complex	19/26 (73.1)	11/14 (78.6)
Enterobacter aerogenes	4/6 (66.7)	9/10 (90.0)
Enterobacter cloacae	19/22 (86.4)	22/28 (78.6)
Escherichia coli	340/419 (81.1)	389/442 (88.0)
Klebsiella oxytoca	21/25 (84.0)	19/22 (86.4)
Klebsiella pneumoniae	72/92 (78.3)	81/100 (81.0)
Proteus mirabilis	8/13 (61.5)	13/15 (86.7)
Proteus vulgaris group	6/7 (85.7)	2/3 (66.7)
Gram-negative other than *Enterobacterales*		
Comamonas testosteroni	5/5 (100)	8/8 (100)
Pseudomonas aeruginosa	51/59 (86.4)	57/62 (91.9)

A patient can have more than 1 pathogen. Multiple isolates of the same species in the same patient are counted only once regardless of source (intra-abdominal or blood) using the isolate with the highest MIC to study drug received.
Source: EU-CTD 2.5, Table 5

2.2.4.2.3. Adverse Events in Complicated Intra-Abdominal Infections: Pooled Phase 2/3 cIAI Studies

Adverse events in patients with cIAI are summarized below. No change to the expected safety profile of ceftazidime were identified by the coadministration of avibactam and metronidazole. Further details are shown in the IB.

Common Adverse Events in cIAI Patients

The incidence of AEs up to the last visit in patients with cIAI was similar between treatment groups [46.4% (398/857 participants) and 44.1% (381/863 participants) in the PF-06947386 plus metronidazole and comparator treatment groups, respectively].

The most common AEs up to the last visit in patients with cIAI in the PF-06947386 plus metronidazole and comparator treatment groups, respectively, were nausea [7.8% (67/857 participants) and 4.1% (35/863 participants)] and diarrhea [7.0% (60/857 participants) and 4.4% (38/863 participants)]; these were similar to the overall patient population in pooled Phase 2/3 cIAI studies.

Intensity

Up to the last visit in patients with cIAI, almost all AEs were mild or moderate in the PF-06947386 plus metronidazole treatment group and the comparator treatment group. The percentages of patients with severe AEs in the same treatment groups were 4.8% (41/857 participants) and 6.3% (54/863 participants), respectively.

The most common severe AEs were generally similar to the overall patient population in pooled Phase 2/3 cIAI studies. Acute kidney injury [0.5% (4/857 participants) and 0.1% (1/863 participants)] was the most common preferred term in the PF-06947386 plus metronidazole treatment group, and respiratory failure [0.4% (3/ 857 participants) and 0.6% (5/857 participants)].

2.3. Benefit/Risk Assessment

Patients enrolled into this clinical study will have cIAI that are of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for cIAI in Japan, in the face of the changing pattern of antibiotic resistance. Risks of participation in the study for each participant are mitigated in that the study patients are closely monitored and will be managed with appropriate therapies as determined by the investigator who is providing treatment.

The risk considerations for this study encompass the known and potential risks for the development product PF-06947386 and its component products ceftazidime and avibactam, as well as the risks associated with other treatments that might be administered as described in this protocol. Other treatments include the marketed product metronidazole. As the risks for these marketed products are widely available in their respective prescribing information, these risks are not discussed within this section.

The full risk profile for ceftazidime is described in the prescribing information for the product (refer to local ceftazidime product labeling). Important risks as laid out in the warnings and precautions in product labeling for ceftazidime include the following:

- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremor, myoclonus, seizures, encephalopathy and coma.

- Antibiotic associated diarrhea, *Clostridioides difficile* diarrhea, colitis, and pseudomembranous colitis.

- Bacterial overgrowth with non-susceptible organisms.

- Inadvertent intra-arterial administration of ceftazidime can result in distal necrosis.

- Hypersensitivity reactions. Though patients with hypersensitivity and serious allergic reactions to cephalosporins, carbapenem or other β-lactam antibiotics are excluded from the trial, first-time episodes of such reactions could occur.

The known and potential risks of receiving the developmental antibiotic combination PF-06947386 are expected to be similar to those seen with ceftazidime and cephalosporins in general. Thus far, no unique risks have been identified for the avibactam component or the combination of ceftazidime and avibactam. However, ceftazidime and avibactam are eliminated via the kidneys, therefore, the dose should be reduced according to the degree of renal impairment. Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment. The risks of ceftazidime and avibactam are considered acceptable.

While it is anticipated that PF-06947386 will have similar efficacy for the treatment of cIAIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the cIAI is determined by the clinical investigator, based on the clinical response of the patients.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06947386 may be found in the IB, which is the SRSD for this study. The SRSD for metronidazole is the Japan Package Insert[5].

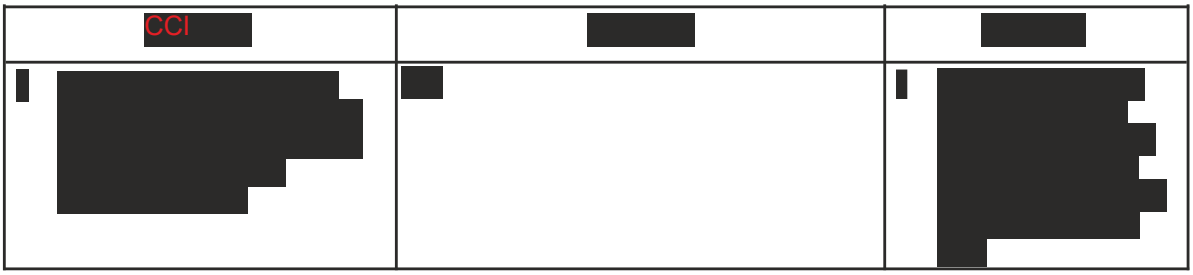
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

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 Table 7. 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 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 Table 7. 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	• Clinical response at the TOC visit

Objectives	Estimands	Endpoints
	details, see Table 7. 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-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Table 7. 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 Table 7. 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.	

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
• To determine the efficacy of PF-06947386 plus metronidazole	• Estimands 6 - 10: the estimands of the secondary endpoints Same as Estimands 1 - 5	• Clinical response at EOT, and LFU visits
• To determine the per-patient microbiological response of PF-06947386 plus metronidazole	• 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 Table 8. Proportion of participants with favorable microbiological response will be calculated. • 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 Table 8. 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 Table 8. All data after intercurrent events of receiving insufficient amount of study	• Per-patient microbiological response at EOT, TOC, and LFU visits

Objectives	Estimands	Endpoints
	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 the treatment of patients with cIAIs	N/A	• AEs and SAEs, all cause mortality, reasons for discontinuations of 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]



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.

4. STUDY DESIGN

4.1. Overall 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.

Approximately 60 participants will be enrolled to study intervention such that there will be approximately 50 evaluable participants in the CE analysis set. Although it is uncertain whether the definition of the sepsis patients subset (Section 9.3) is met at the timing of study entry, 3 to 5 enrolled participants are anticipated to meet the definition of the sepsis patients subset.

Note: "Enrolled" means a participant's, or his or her legally authorized representative'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.

To be eligible to enroll in this study, participants must have cIAI at Screening visit. The full list of eligibility criteria for the study is included in Section 5.

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 (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.

4.2. Scientific Rationale for Study Design

Japanese patients were enrolled in the two multinational, multicenter, randomized, double-blind, comparative studies in cUTI and HAP/VAP patients which were conducted as pivotal studies for PF-06947386. On the other hand, Japanese patients were not enrolled in the studies in cIAI patients.

Since the efficacy and safety have been confirmed in clinical studies in cUTI and HAP/VAP patients, including Japanese patients, as representative diseases, this study is being conducted to evaluate the efficacy and safety in Japanese cIAI patients as a multicenter, open-label, single-arm study in accordance with the Guidelines for Clinical Evaluation of Antibacterial Drugs.

Human reproductive safety data are limited for PF-06947386, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

The dose of PF-06947386 was selected on the basis of achieving pre-determined exposure targets for both ceftazidime and avibactam simultaneously in at least 90% of patients. These exposure targets were based on the activity of PF-06947386 in surveillance studies and nonclinical PK/PD studies.

The exposure target for ceftazidime was achieving or exceeding a free systemic ceftazidime concentration of 8 mg/L for at least 50% of the dosing interval (50% *f*T> PF-06947386 MIC of 8 mg/L). A PF-06947386 MIC of 8 mg/L was chosen because it was observed to include MICs obtained against ≥90% of clinical isolates of *Enterobacterales* and *P. aeruginosa* in contemporary global surveillance studies. Specifically, the PF-06947386 MIC_{90} against *P. aeruginosa* was 8 mg/L in multiple studies, and the MIC_{90} values against unselected clinical isolates of species of *Enterobacterales* were 1 mg/L or lower. The exposure target for avibactam was achieving or exceeding a free systemic avibactam concentration of 1 mg/L for 50% of the dosing interval (50% *f*T>C_T of 1 mg/L). The 1 mg/L exposure target for avibactam was a critical C_T that was determined from nonclinical *in vitro* and *in vivo* experiments.

Population PK models of ceftazidime and avibactam were developed using data from the Phase 1 PF-06947386 and ceftaroline fosamil-avibactam studies, along with the data collected in patients with cUTI and cIAI in the Phase 2 and Phase 3 PF-06947386 studies. These population PK models of ceftazidime and avibactam were then used to explore PK/PD relationships in the Phase 2 and Phase 3 studies and to conduct simulations to evaluate the PTA, using the targets outlined above. The PTA analyses were used to support dose adjustments for PF-06947386 in patients with renal impairment and PF-06947386 breakpoints. Susceptibility interpretive criteria of *Enterobacterales* and *P. aeruginosa* for PF-06947386 are ≤8 mg/L, respectively.

In summary, dose selection and breakpoint justification was based on a prediction of 90% of the patient population achieving exposures that simultaneously maintained 50% *f*T> PF-06947386 MIC of 8 mg/L for ceftazidime and 50% *f*T>C_T of 1 mg/L for avibactam.

The population PK models of ceftazidime and avibactam (CAZ-MS-09) were used to calculate individual PK profiles of ceftazidime and avibactam for patients with cIAI from the Phase 3 studies RECLAIM, RECLAIM3, and REPRISE where individual exposure prediction was available. In >90% of patients, exposure exceeded the joint PK/PD targets (50% *f*T>MIC for PF-06947386 MIC up to 8 mg/L for ceftazidime and 50% *f*T>C_T of 1 mg/L for avibactam) derived from nonclinical studies. Using the same population PK model to simulate exposures of 5000 patients with cIAI, the joint PTA against the PK/PD targets was >90% up to PF-06947386 MIC of 8 mg/L.

Taken together, the results of the studies in cIAI validate that the proposed dose achieves adequate exposure in the majority of patients with normal renal function and is associated with therapeutic efficacy.

A dose regimen of 2.0 g ceftazidime plus 0.5 g avibactam given as a 2 hour IV infusion, q8h, for patients with normal renal function has been demonstrated to be an effective dose for the treatment of patients with cIAI. This dose regimen is the approved dose in other regions and would provide the comparable exposures and PTA between non-Japanese and Japanese patients based on the data from population PK and PK/PD analysis. Furthermore, this dose is predicted to be effective against at least 90% of isolates of *Enterobacterales* and *P. aeruginosa,* which are the pathogens for which PF-06947386 will provide the most benefit. Each doses for patients with renal impairment (Section 6.1.1.2) is predicted to achieve in ≥94.9% of patients the exposure targets for efficacy against isolates of *Enterobacterales* and *P. aeruginosa* with a PF-06947386 MIC of up to 8 mg/L, which are the pathogens for which PF-06947386 will provide the most benefit.

The proposed PF-06947386 dose regimens overall support the following breakpoint with a ≥90% PTA for patients with cIAI, cUTI, and HAP/VAP:
MIC of 8 mg/L for *Enterobacterales* and *P. aeruginosa* for the PK/PD target of 50% *f*T>PF-06947386 MIC for ceftazidime and 50% *f*T>C_T of 1 mg/L for avibactam.

The dose of metronidazole for intra-abdominal infections is within the dosage which approved in Japan.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Age ≥20 years at the time of the Screening visit.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Must have clinical evidence of cIAI as follows:

    i. Preoperative enrollment where the following clinical criteria are met with confirmation of infection by surgical intervention within 24 hours of entry:

    a. Requirement for surgical intervention, defined per protocol as open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery

    b. Evidence of systemic inflammatory response, with at least one of the following:

    - Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
    - Elevated white blood cells (>12000 cells/mm^3)
    - Drop in blood pressure (however, systolic blood pressure must be >90 mmHg without pressor support)
    - Increased heart rate (>90 bpm) and respiratory rate (>20 breaths/min)
    - Hypoxia

- Altered mental status

c. Physical findings consistent with intra-abdominal infection, such as:

- Abdominal pain and/or tenderness, with or without rebound
- Localized or diffuse abdominal wall rigidity
- Abdominal mass

d. Supportive imaging findings of intra-abdominal infection such as perforated intraperitoneal abscess detected on computed tomography scan, magnetic resonance image, or ultrasound.

e. Intention to send specimens from the surgical intervention for culture.

ii. Intra-operative/post-operative enrollment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. Specimens from the surgical intervention must be sent for culture. Patients who undergo a surgical procedure with complete fascial closure are appropriate for the trial. The skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished. The patient must have at least one of the following diagnosed during the surgical intervention:

a. Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall

b. Diverticular disease with perforation or abscess

c. Appendiceal perforation or peri-appendiceal abscess

d. Acute gastric or duodenal perforations, only if operated on >24 hours after perforation occurs

e. Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs

f. Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)

g. Intra-abdominal abscess (including of liver or spleen provided that there is extension beyond the organ with evidence of intraperitoneal involvement)

To note,
Participants who meet the following clinical and microbiological criteria are considered to have sepsis in this protocol:

Clinical: Total score ≥2 in SOFA for ICU patients, 2 items or more in qSOFA for non-ICU patients (Section 10.7)

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.

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Participant is diagnosed with traumatic bowel perforation undergoing surgery within 12 hours; perforation of gastroduodenal ulcers undergoing surgery within 24 hours. Other intra-abdominal processes in which the primary etiology is not likely to be infectious.

2. Participant has abdominal wall abscess or bowel obstruction without perforation or ischemic bowel without perforation

3. Participant has simple cholecystitis, or simple appendicitis, or infected necrotizing pancreatitis, or pancreatic abscess

4. Participant whose surgery will include staged abdominal repair, or "open abdomen" technique, or marsupialization. This criterion is intended to exclude participants in whom the abdomen is left open, particularly those for whom reoperation is planned.

5. Participant is known at study entry to have cIAI caused by pathogens resistant to the study antimicrobial agents

6. Participant has evidence of sepsis with shock not responding to IV fluid challenge or anticipated to require the administration of vasopressors for >24 hours

7. Participant has perinephric infections

8. Participant is receiving hemodialysis or peritoneal dialysis, or has indwelling peritoneal dialysis catheter

9. Participant has suspected intra-abdominal infections due to fungus, parasites (eg, amebic liver abscess), virus, or tuberculosis

10. Participant has a known history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to cephalosporin antibiotics or other β-lactam antibiotics or metronidazole

11. Participant is considered unlikely to survive the 6- to 8-week study period or has a rapidly progressive or terminal illness

12. Participant with concurrent infection that may interfere with the evaluation of response to the study antibiotic

13. Participant has past (prior 6 months) or current history of acute hepatitis. Participant has past or current history of chronic hepatitis, cirrhosis, acute hepatic failure, and/or acute decompensation of chronic hepatic failure.

14. Participant has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood

15. Participant is chronically immunocompromised as evidenced by any of the following:

    a. Human immunodeficiency virus infection, with either a current acquired immune deficiency syndrome defining condition (eg, Kaposi's sarcoma, *Pneumocystis carinii* pneumonia) or a CD4+ T lymphocyte count <200/mm^3 at the time of study entry

    b. Metastatic or hematological malignancy requiring chemotherapeutic interventions within 6 weeks prior to first IV infusion

    c. Immunosuppressive therapy for organ transplantation

16. Participant is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study.

17. Participant has known inflammatory bowel disease (ulcerative colitis or Crohn's disease)

18. Participant has known or suspected *Clostridioides difficile* associated diarrhea

19. Participant is pregnant or breastfeeding. A serum β-hCG pregnancy test must be conducted for women of childbearing potential at Screening visit. If the results of the serum β-hCG cannot be obtained prior to dosing of IP, a participant may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must

still be obtained. If either test is positive, the participant must be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant sexual history, including methods of contraception, should be considered. Any participant whose sexual history suggests the possibility of early pregnancy must be excluded.

20. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

21. Participant needs effective concomitant systemic antibacterials (eg, oral, IV, or intramuscular) or systemic antifungals in addition to study regimens, except vancomycin, linezolid, or daptomycin if started for known or suspected MRSA or *Enterococcus* species as per protocol Section 6.5

22. Participant has received systemic antibacterial agents within the 72-hour period prior to study entry, unless either of the following pertains:

    a. Participant has a new infection (not considered a treatment failure) and both of the following are met:

        - Participant received no more than 24 hours of total prior antibiotic therapy
        - Participant received ≤1 dose of a treatment regimen post operatively and antibiotics were not received more than 6 hours post procedure (defined as 6 hours from the time of skin closure or, if skin closure was not performed, 6 hours from the time the wound dressing was applied)

    b. Participant is considered to have failed the previous treatment regimen. In this case, preoperative treatment of any duration with non-study systemic antimicrobial therapy for peritonitis or abscess is permitted provided that all of the following are met:

        - The treatment regimen has been administered for at least 72 hours and is judged to have failed.
        - The participant has an operative intervention that is just completed or is intended no more than 24 hours after study entry.
        - Findings of infection were documented at surgery.
        - Specimens for bacterial cultures and susceptibility testing are taken at operative intervention

- No further non-study antibacterials are administered after first IV infusion.

c. Participant has received systemic antibiotic agents no more than 24 hours (no more than one daily dose) within the 72-hour period prior to study entry.

23. Use of potent inhibitors of organic anion transporters OAT1 and/or OAT3 (eg, probenecid, or PAH) are prohibited.

24. Participant has previously been treated with ceftazidime-avibactam.

Prior/Concurrent Clinical Study Experience:

25. Participant is participating in any other clinical study that involves the administration of an investigational medication at the time of presentation, during the course of the study, or who has received treatment with an investigational medication in the 30 days prior to study enrollment.

26. Participant had been previously enrolled in this study

Diagnostic Assessments:

27. Estimated CrCL ≤50 mL/min calculated by Cockcroft-Gault method[6]. Refer to Appendix 8 for calculating estimated CrCL.

28. Hematocrit <25% or hemoglobin <8 g/dL

29. Absolute neutrophil count <1000/mm^3

30. Platelet count <75000/mm^3

31. Bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related to the acute infection or known Gilbert's disease

32. ALT or AST >3 × ULN values at Screening. Participants with elevations of AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and directly related to the infectious process being treated. This must be documented.

33. Alkaline phosphatase >3 × ULN. Participants with values >3.0 × ULN and <5.0 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

Other Exclusions:

34. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

Not applicable.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to PF-06947386 and metronidazole.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06947386 (ceftazidime-avibactam)	Metronidazole
Type	Drug	Drug
Dose Formulation	Powder for concentrate for solution for infusion	Solution for injection

Unit Dose Strength(s)	2.0 g ceftazidime and 0.5 g avibactam	0.5 g
Route of Administration	Intravenous	Intravenous
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.

6.1.1. Administration

Patients will receive PF-06947386 (2.0 g of ceftazidime and 0.5 g of avibactam) intravenously, immediately followed by an IV administration of metronidazole (0.5 g). Participants will receive a minimum of 5 full days (15 doses) of IV study intervention up to a maximum of 14 full days (42 doses) of study intervention.

The first dose of IV study intervention is given at Visit 2 on Study Day 1.

Dosing intervals for patients with normal renal function and mild renal impairment are described in Section 6.1.1.1.

For patients enrolled into the study whose CrCL drops to ≤50 mL/min while on IV study intervention, follow the instructions in Section 6.1.1.2.

6.1.1.1. Dosing Intervals in Patients With Normal Renal Function and Patients With Mild Renal Impairment (CrCL >50 mL/min)

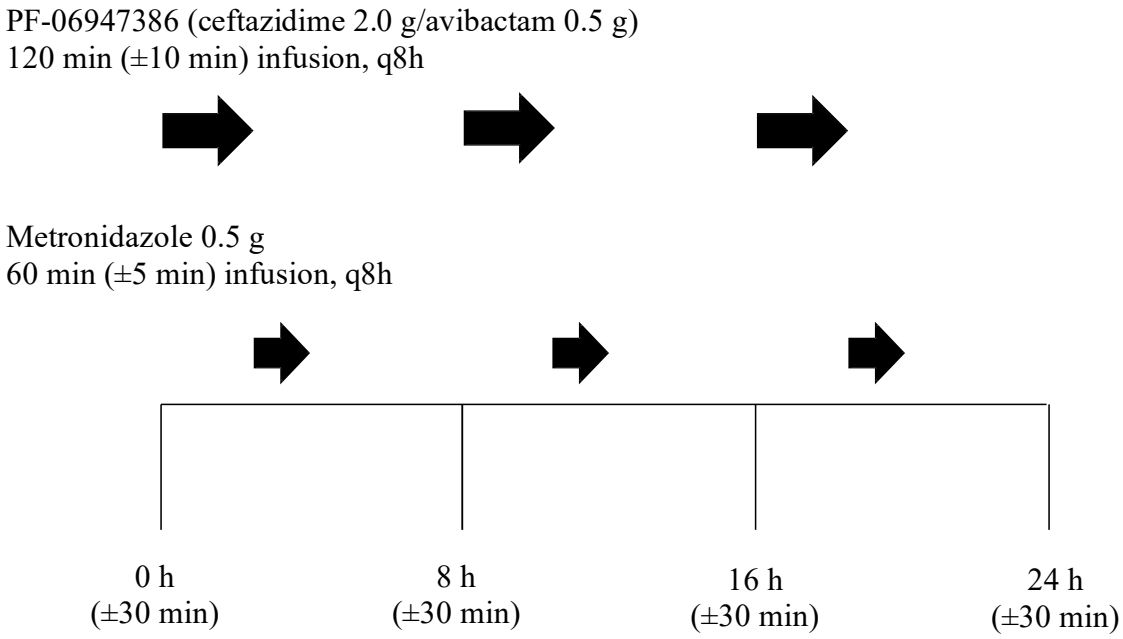
IP will be administered q8h (±30 minutes) as described in Figure 2.

Table 5. Ceftazidime/Avibactam Adjustments for Patients With Normal Renal Function and Patients With Mild Renal Impairment

CrCL (mL/min)[a]	Investigational product	Dose, interval, duration
Normal or Mild impairment: (>50)	PF-06947386 (ceftazidime-avibactam)	2.0 g ceftazidime/ 0.5 g avibactam q8h ±30 minutes over 120 minutes ±10 minutes at a constant rate of infusion
	Metronidazole	Metronidazole 0.5 g q8h ±30 minutes over 60 minutes ±5 minutes at a constant rate of infusion

a. Estimated CrCL using Cockcroft-Gault formula (Section 10.8).

Figure 2. Schematic of Dosing Intervals for Patients With Normal Renal Function /Mild Renal Impairment (for an Arbitrary 24 Hour Period)



If necessary, a 1-time dosing interval adjustment is allowed after the first dose of IV study intervention to create a suitable dosing schedule going forward with an 8-hour (±30 minutes) dosing interval. The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a 1-time 4-hour dosing interval is allowed between the first and the second dose). If a 1-time dose interval adjustment is implemented for the second dose, all further dosing times will be calculated based on the time of the second dose.

For example, if the first dose is started at 10 AM, the second dose would be due at 6 PM. A 1-time adjustment of dosing time would allow the second dose to be started between 2 PM and 6 PM. All future doses would be given at 8 hours (±30 minutes) from the time the second dose was actually administered. If the timing of a dose fluctuates from the scheduled time (eg, started 15 minutes early for a dose scheduled for 4 PM), the next dose should still be administered 8 hours from the scheduled dose, which would be 12 AM.

6.1.1.2. Dose Regimen Adjustments for Patients Whose CrCL Drops ≤50 mL/min While on IV Study Intervention

If a patient's estimated CrCL falls below the threshold for study inclusion, subsequent to study entry and while still on IV study intervention, retesting should be performed promptly.

Because the CrCL determination is only an estimate of renal function, in instances where the CrCL is below 50 mL/min, the investigator should use his or her discretion in determining

whether an immediate dose adjustment, a short period of continued observation, or discontinuation of therapy is warranted. Once a dose adjustment is decided upon, the investigator should inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments as outlined in Table 6.

Since a decline in renal function may be transient, CrCL should be closely monitored in patients demonstrating renal dysfunction at any point before or during the study to ensure that therapeutic doses are being administered.

Table 6. Dose Regimens and Infusion Times for Patients Whose Estimated CrCL Drops Below 50 mL/min While on IV Study Intervention

CrCL (mL/min)[a, b]	Investigational product	Dose, interval, duration
50 to 31	PF-06947386 (ceftazidime-avibactam)	1 g ceftazidime/ 0.25 g avibactam q8h ±30 minutes over 120 minutes ±10 minutes at a constant rate of infusion
	Metronidazole	Metronidazole 0.5 g q8h ±30 minutes over 60 minutes ±5 minutes at a constant rate of infusion
30 to 16	PF-06947386 (ceftazidime-avibactam)	0.75 g ceftazidime/ 0.1875 g avibactam every 12 hours ±30 minutes over 120 minutes ±10 minutes at a constant rate of infusion
	Metronidazole	Metronidazole 0.5 g q8h ±30 minutes over 60 minutes ±5 minutes at a constant rate of infusion
15 to 6	PF-06947386 (ceftazidime-avibactam)	0.75 g ceftazidime/ 0.1875 g avibactam every 24 hours ±30 minutes over 120 minutes ±10 minutes at a constant rate of infusion
	Metronidazole	Metronidazole 0.5 g q8h ±30 minutes over 60 minutes ±5 minutes at a constant rate of infusion
< 6	PF-06947386 (ceftazidime-avibactam)	0.75 g ceftazidime/ 0.1875 g avibactam every 48 hours ±30 minutes over 120 minutes ±10 minutes at a constant rate of infusion
	Metronidazole	Metronidazole 0.5 g q8h ±30 minutes over 60 minutes ±5 minutes at a constant rate of infusion

a. Estimated CrCL using Cockcroft-Gault formula (Section 10.8).
b. PF-06947386 and metronidazole are removed by hemodialysis. Dosing of PF-06947386 and metronidazole on hemodialysis days should occur after completion of hemodialysis. In cases where hemodialysis is needed but scheduling the dosing of PF-06947386 and metronidazole after completion of hemodialysis is not feasible, or if the investigator has concerns for the participant to continue with dosing, discontinuation from study treatment may be considered, as needed.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once reconstituted or diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label, single-arm study.

Following full assessment and determination that the participant meets all eligibility criteria, the investigator or designee may administer IP to the participant.

The investigator or designee will fax or email a completed registration form to the sponsor. The investigator or designee shall receive the enrollment number from the sponsor via fax or email.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.5. Concomitant Therapy

All prescription, over-the-counter medications, and dietary and herbal supplements being taken by the patient during the 30 days prior to first IV infusion (considered prior treatment) and from first IV infusion through study end (considered concomitant treatments) must be documented on the appropriate pages of the eCRF. Medications that are considered to maintain their effect during the 30 days prior to first infusion, such as medications with long dosing intervals, must be documented on the appropriate pages of the eCRF even if they are taken more than 30 days prior to first IV infusion. Systemic antibiotics should be

documented for the entire duration of the study (from 30 days prior to first IV therapy through study end).

Surgical history will be collected at Screening. Non-drug procedures conducted during the 30 days prior to first IV infusion (considered prior treatment) and from first IV infusion through study end (considered concomitant treatments) must be documented on the appropriate pages of the eCRF.

If *Enterococcus* species or MRSA is one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy is indicated, then vancomycin, linezolid, or daptomycin may be added to study regimens according to the usual practice of the investigator. If vancomycin, linezolid, or daptomycin is started empirically to cover MRSA or *Enterococcus* species, and if final culture results did not isolate MRSA or *Enterococcus* species, then the investigator should discontinue the additional Gram-positive coverage that was empirically added.

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. However, if a new infection develops at a remote site (ie, outside of the abdomen) between the date and time of first IV infusion and study end, and the investigator considers addition of nonstudy antibiotics essential to the safety and wellbeing of the patient, additional antibiotics may be added. If possible, the investigator should attempt to choose antibiotics that will not have antibacterial activity against the patient's cIAI baseline pathogens to avoid confounding the assessment of the effect of study intervention. Antibiotic peritoneal lavage is not permitted (peritoneal lavage with saline or other nonantibacterial containing solution is allowed). Topical antibacterial and topical antifungals are permitted except that they may not be applied to the surgical site. It is anticipated that in instances of clinical failure, alternative "rescue" antibacterial therapy to treat the cIAI would be instituted. Systemic antifungal therapy should be avoided unless clinically indicated. A known requirement for antifungal therapy at first IV infusion would exclude the patient from enrollment based on exclusion criterion 21.

Other medications, which are considered necessary for the patients' safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after starting IV study intervention, the investigator should contact the Pfizer Medical Monitor or designee before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have completed IV study intervention and are in the follow-up period should remain in the study as they are not actively on IV study intervention but being followed for outcomes.

Use of potent inhibitors of organic anion transporters OAT1 and/or OAT3 (eg, probenecid, or PAH) are prohibited during the study because they have the potential to alter (decrease) the clearance of avibactam when coadministered.

In this study, metronidazole is also administered in combination with PF-06947386. Therefore, the package insert of the metronidazole should also be referred to for the precautions regarding co-administration.

6.6. Dose Modification

For patients enrolled into the study whose CrCL drops to ≤50 mL/min while on IV study intervention, follow the instructions in Section 6.1.1.2.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Request by the participant or legally authorized representative to terminate treatment
- Investigator judgment that continued dosing is not in the best interest of the participant
- Request by the Sponsor to terminate treatment
- Anaphylaxis or other serious allergic reaction to the study intervention, or other AEs or confirmed laboratory abnormality, judged by the investigator to be a significant safety concern
- Positive pregnancy test at any time during the study treatment period

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;

- Study terminated by sponsor;

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately maximum 185 mL. The actual collection times of blood sampling may change. If blood culture is positive at Baseline, additional samples will be collected. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. APACHE II Score

APACHE II score will be calculated APACHE II score using most recent local laboratory results at Screening (see Section 10.6). Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. If ABG is not clinically indicated, the APACHE II score should be calculated using serum bicarbonate and oxygenation should be presumed normal.

8.1.2. Imaging Test

Imaging tests are not required for the study, but the results should be submitted if done as part of the diagnosis. Imaging tests include plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

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8.1.6. Clinical Response

Clinical response definitions at the EOT, TOC, LFU, and Early Termination/Discontinuation visits are cure, failure, and indeterminate. Reasons for failure will be indicated according to the clinical response definitions in Table 7. If a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

Table 7. 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.

Table 7. Definitions of Clinical Response at the EOT, TOC, LFU, and Early Termination/Discontinuation Visits

Clinical response	Definition
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

8.1.6.1. Adjudication Committee

The adjudication committee will consist of 2 or more external infectious disease specialists especially intra-abdominal infection. The adjudication committee will review investigators' clinical assessments based on the collected data (imaging test results if available, signs and symptoms of intra-abdominal infection, wound examination, temperature, WBC, CRP, and microbiological data, description of operative procedure, investigator case summary, operative notes, discharge summary) for consistency of evaluation in the study. The data are reviewed with masking the information of the site and the investigator to avoid biases. The committee would request to the principal investigator (or subinvestigator) to provide other information as necessary. If a discrepancy exists after the data are cleaned, the assessment by the adjudication committee will prevail. In addition, patients assessed by the adjudication committee as having inadequate initial infection source control will be re-classified as indeterminate and will be excluded from the CE and ME analysis sets.

All required documentation including surgical reports and imaging results may be submitted if requested by the Adjudication Committee.

There may be instances when copies of medical records to support the adjudication committee review are requested by Pfizer. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of medical records before submission to Pfizer.

8.1.7. Microbiological Assessments

8.1.7.1. Blood Culture

Blood cultures must be obtained at Screening. If blood cultures are positive, the assessment is to be repeated upon knowledge of a positive result until sterilization is confirmed in accordance with the SoA for the timing and frequency. As a general rule, culture and organism identification should be performed at the local or regional laboratory unless there are difficulties to conduct the procedures at the study site, but it is acceptable to use the central laboratory. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of blood culture or isolates.

8.1.7.2. Culture of Abdominal Infection Site

Cultures must be obtained at initial qualifying procedure [performed within 24 hours of entry for preoperative enrollment (see Section 5.1, inclusion criterion 3)]. If additional procedures are performed, additional abdominal site cultures should be obtained. Cultures from the wound/procedure site should be obtained only if clinically indicated through study end. As a general rule, Gram stain (if applicable), culture and organism identification should be performed at the local or regional laboratory unless there are difficulties to conduct the procedures at the study site, but it is acceptable to use the central laboratory. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study specific microbiology and clinic laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of other specimens/tissues for culture or isolates.

8.1.8. Microbiological Response Assessments

The per-patient and per-pathogen microbiological response of PF-06947386 plus metronidazole in mMITT and ME analysis sets for patients with cIAI at the EOT, TOC, LFU, and Early Termination/Discontinuation visits is a secondary outcome. If a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

Microbiological response will be assessed per-patient and per-pathogen according to the definitions listed below. It is based on outcome per-pathogen isolated at the initial visit (considered as causative) and on the isolation of pathogens during the course of treatment or the post treatment period.

8.1.8.1. Per-Pathogen Microbiological Assessments After Completion of All Follow-up Visits

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 8. Microbiological responses other

than "indeterminate" will be classified as "favorable" or "unfavorable". Favorable microbiological response assessments include "eradication", "presumed eradication" and "colonization". Unfavorable microbiological response assessments include "persistence", "persistence with increasing MIC", and "presumed persistence". Patients with a microbiological response assessment of "indeterminate" will be considered to be nonevaluable for the ME analysis set. "Superinfection" and "new infection" will be considered separately (Table 9).

8.1.8.2. Per-Patient (Overall) Microbiological Response Assessments

Overall microbiological response will also be assessed as "favorable" or "unfavorable" for each patient. "Eradication" and "presumed eradication" as well as "colonization" will be considered as "favorable" microbiological response in the analyses.

For patients from whom only 1 causative pathogen is isolated, the overall microbiological response assessment will be based on the microbiological response assessment for that pathogen.

For patients from whom more than 1 baseline pathogen is isolated, the overall microbiological response assessment will be "favorable" only if the microbiological response assessment for each of the baseline pathogens isolated is "favorable".

8.1.8.3. Microbiological Response

Per-pathogen microbiological response and per-patient microbiological response will be categorized according to the definitions in Table 8.

Table 8. 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.

Table 8. Microbiological Response Categories at Day 1 (Baseline), EOT, TOC, LFU, and Early Termination/Discontinuation Visits

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.

Microbiological response for blood pathogens should be classified similarly to the classifications for baseline pathogens noted in Table 8.

8.1.8.4. MIC Among Pathogens

The clinical cure and per-pathogen microbiological response at the EOT, TOC, and LFU visits will be evaluated for MIC categories. The MIC categories to be used are: <0.008, 0.015, 0.03, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and >256 µg/mL.

8.1.8.5. Emergent Infections

Pathogens first appearing after Baseline in patients with a baseline pathogen are categorized in Table 9 and will be summarized separately.

Table 9. 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.

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8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Medical and Surgical History, Medication History

Medical history and surgical history will be collected at Screening. Complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected.

8.2.2. Height and Weight

Height and weight will be measured at Screening visit. Recently measured height and weight results may be used if patient is not ambulatory at the time of Screening. Body mass index will be calculated. After the Screening visit, weight should be measured as clinically indicated.

8.2.3. Pulse Rate, Blood Pressure, Respiratory Rate

Pulse rate, blood pressure, and respiratory rate will be measured at Screening, Day 1 (Baseline), daily during treatment with study intervention, and EOT, TOC, LFU, and Early Termination /Discontinuation visits (SoA). A semiautomatic blood pressure recording device should be used where available, with an appropriate cuff size. The patients will be required to rest in a supine position for at least 5 minutes prior to pulse rate and blood pressure measurements. Respiratory rate will be collected in breaths per minute.

8.2.4. Heart Rate

Heart rate will be measured at Screening. Heart rate may be evaluated either in the 12-lead ECG or in the monitor ECG.

ECG values of potential clinical concern are listed in Appendix 9.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.

At Screening visit, 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. The participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until study end.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with

authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Cardiovascular and death events will be reported according to AE reporting procedures.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-06947386 and metronidazole greater than daily dose of study intervention defined in Section 6.1.1 within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose. To note, both ceftazidime and avibactam can be partially removed by hemodialysis.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06947386 and metronidazole (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 12 hours from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected for measurement of plasma concentrations of ceftazidime and avibactam as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample and initiation/end of each infusion will be recorded.

All efforts will be made to obtain 3 samples, 1 from each of the 3 time windows, for each participant for PK sample collection as specified in the SoA. Missed collection of samples or collection of samples outside of the allowed window will not be captured as protocol deviations, as long as the exact time of the collection is noted in the source documents and the CRF. Blood for PK must NOT be drawn from the same arm used for IV drug administration.

Samples will be used to evaluate the PK of ceftazidime and avibactam. CCI [redacted]

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of ceftazidime and avibactam will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Ceftazidime is a β-lactam antimicrobial agent, and it is expected that the time that the plasma concentration of ceftazidime exceeds the MIC (%T >MIC) of the infecting organism will be correlated with efficacy. Thus, the %T >MIC, will be calculated from an appropriate PK model after the ceftazidime plasma concentrations are collected and analyzed. The collection of ceftazidime plasma concentrations is described in Section 8.5, and the detailed method to calculate %T >MIC will be included in the separate PK/PD analysis plan.

It is assumed that the percentage above a threshold concentration of avibactam is associated with avibactam's effect on inhibiting β-lactamase. An appropriate PK/PD index for avibactam, such as the percentage of time above a threshold concentration (%T > the critical threshold concentration of avibactam), will be calculated with a PK model after avibactam plasma concentrations are collected and analyzed. The collection of avibactam plasma concentration is described in Section 8.5, and the detailed method to calculate avibactam exposure measures will be included in the separate PK/PD analysis plan.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimens for Genetics are not collected in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Banked Biospecimens for Biomarkers

Banked biospecimens for Biomarkers are not collected in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

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%.

9.1.1. Estimands

Estimand 1: This estimand will be the primary estimand of the primary endpoint and will be the estimated average treatment effect on the clinical response at TOC visit for PF-06947386 + metronidazole for all 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 Table 7. 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 2: This estimand will be the supportive estimand of the primary endpoint and will be the estimated average treatment effect on the clinical response at TOC visit for PF-06947386 + metronidazole for all 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 Table 7. Proportion of participants with clinical cure will be calculated.

Estimand 3: This estimand will be the supportive estimand of the primary endpoint and will be the estimated average treatment effect on the clinical response at TOC visit for PF-06947386 + metronidazole for all 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 Table 7. Proportion of participants with clinical cure will be calculated.

Estimand 4: This estimand will be the supportive estimand of the primary endpoint and will be the estimated average treatment effect on the clinical response at TOC visit

for PF-06947386 + metronidazole for all 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-abdominal infection, or additional antibiotics for ongoing symptoms of intra-abdominal infection etc. will be regarded as a failure clinical response. For details, see Table 7. 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: This estimand will be the supportive estimand of the primary endpoint and will be the estimated average treatment effect on the clinical response at TOC visit for PF-06947386 + metronidazole for all 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 Table 7. 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.

Estimands 6-10: These estimands will be the same estimands as Estimands 1-5 but these estimands will be the estimands of the secondary endpoints and will be the estimated average treatment effects on the clinical response at EOT, and LFU visits.

Estimand 11: This estimand will be the estimand of the secondary endpoints and will be the estimated average treatment effects on the per-patient microbiological response at EOT, TOC, and LFU visits for PF-06947386 + metronidazole for all 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 Table 8. Proportion of participants with favorable microbiological response will be calculated.

Estimand 12: This estimand will be the estimand of the secondary endpoints and will be the estimated average treatment effects on the per-patient microbiological response at EOT, TOC, and LFU visits for PF-06947386 + metronidazole for all 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 Table 8. 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: This estimand will be the estimand of the secondary endpoints and will be the estimated average treatment effects on the per-patient microbiological response at EOT, TOC, and LFU visits for PF-06947386 + metronidazole for all 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 Table 8. 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.

Estimands 14-16: These estimands will be the same estimands as Estimands 11-13 but these estimands will be the estimands of the secondary endpoints and will be the estimated average treatment effects on the per-pathogen microbiological response at EOT, TOC, and LFU visits.

9.2. Sample Size Determination

In the previous global Phase 3 studies for cIAI (RECLAIM and RECLAIM3), the point estimate of proportion of patients with clinical cure at TOC visit in the CE analysis set was approximately 90% in both ceftazidime-avibactam + metronidazole and active comparator (meropenem) treatment groups.

The threshold value will be set to 78% which is calculated by subtracting the non-inferiority margin of both studies 12.5% from the proportion of patients with clinical cure. When the point estimate of proportion of patients with clinical cure at TOC visit in the CE analysis set becomes greater than or equal to the threshold value, the efficacy is considered to be shown in this study. The expected value of proportion of patients with clinical cure is greater than or equal to 78% in this study, it is considered that this drug would contribute as one of the antibacterial drugs.

When 60 patients are treated, the CE analysis set at TOC visit will have approximately 50 evaluable patients based on the results of the previous studies. Under the assumption of 50 patients in the CE analysis set at TOC visit and 90% of true proportion of patients with clinical cure, the probability of meeting the criterion stated above is approximately 99%.

In addition, causal pathogens are relatively easy to detect because patients with cIAI are often treated with drainage. When 60 patients are treated, it is considered that a considerable number of strains can be collected for species in which clinical isolation is relatively rare.

Although it is uncertain whether the definition of the sepsis patients subset (Section 9.3) is met at the timing of study entry, 3 to 5 enrolled participants are anticipated to meet the definition of the sepsis patients subset.

9.3. Analysis Sets

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 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 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 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 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 (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.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

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.

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

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

9.4.2. Primary Endpoint(s)

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

The proportion and the 95% CI will be calculated. The primary analysis will be performed on the CE analysis set. Supplemental analyses will be performed on the MITT, mMITT, ME, and eME analysis sets.

9.4.3. 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
- AEs and SAEs, all cause mortality, reasons for discontinuations of IV study intervention and study, vital sign measurements, and potentially clinically significant changes in laboratory parameters during the entire study
- Ceftazidime and avibactam plasma concentrations by nominal sampling window
- For patients with sepsis, selected efficacy and safety endpoints from endpoints for the overall population

For clinical response at each visit, the proportion and the 95% CI will be calculated. Analyses will be performed on the CE, MITT, mMITT, ME, and eME analysis sets.

For a favorable per-patient or per-pathogen microbiological response at each visit, the proportion and the 95% CI (per-patient only, when N is enough to calculate) will be calculated. Patients with "Indeterminate" are not included in the denominator. Analyses will be performed on the mMITT, ME, and eME analysis sets.

AEs and SAEs (including local tolerability), discontinuations, and changes in vital signs, and clinical laboratory parameters will be descriptively summarized, and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data.

All safety analyses will be performed on the safety population.

Ceftazidime and avibactam plasma concentrations by nominal sampling window will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation. 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.

For patients with sepsis, safety and efficacy will be investigated. Analyses will be performed in the sepsis patients subset and the sepsis evaluable patients subset.

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

9.5. Interim Analyses

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.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an adjudication committee. The adjudication committee is independent of the study team and includes only external members. The adjudication committee will consist of 2 or more external infectious disease specialists especially intra-abdominal infection. The adjudication committee charter describes the role of the adjudication committee in more detail. The adjudication committee will review investigators' assessments, including clinical response, based on the collected data for consistency of evaluation in the study. If a discrepancy exists between the adjudication committee and investigators, the assessment by the adjudication committee will prevail. For details, see Section 8.1.6.1

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or his or her legally authorized representative must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant or his or her legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan and contracts.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore

intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this 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 10. 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.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events

(AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 7 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Intrauterine device.
2. Intrauterine hormone-releasing system.
3. Bilateral tubal occlusion.
4. Vasectomized partner:

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

5. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

6. Male or female* condom with or without spermicide*.

7. Cervical cap*, diaphragm*, or sponge with spermicide*.

8. A combination of male condom with either cervical cap*, diaphragm*, or sponge with spermicide* (double-barrier methods).

* Not approved in Japan

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: APACHE II Classification System

Table 11. APACHE II Score Form

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE +4	+3	+2	+1	0	LOW ABNORMAL RANGE +1	+2	+3	+4
1. Temperature (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2. Mean arterial pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
3. Heart rate (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
4. Respiratory rate (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
5. Oxygenation A-aDO_2 or PaO_2 (mmHg) a) FiO_2 ≥0.5:record A-aDO_2	≥500	350-499	200-349		<200				
b) FiO_2 <0.5:record only PaO_2					>70	61-70		55-60	<55
6. Arterial pH - If no ABGs record Serum HCO_3 below*	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
7. Serum Sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
8. Serum Potassium (mmol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9. Serum Creatinine (mg/dL) Double point score for acute renal failure	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10. Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
11. White Blood Count (k/mm^3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
12. Glasgow Coma Scale (Score = 15 minus actual GCS)	15-GCS=								
A. Total Acute Physiology Score (APS)				**Sum of the 12 individual points=**					
* Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

Table 11. APACHE II Score Form (Continued)

Glasgow Coma Scale (Eyes, Motor, and Verbal)	B Age points		C Chronic Health points		APACHE II Score
Eyes open	≤44	0	If any of the 5 chronic health evaluation		APACHE II Score
4 - spontaneously	45-54	2	categories is answered yes give +5 points for non-		= A: APS points
3 - to speech	55-64	3	operative or emergency postoperative patient and		+ B: Age points
2 - to pain	65-74	5	give +2 points if elective postoperative patient		+ C: Chronic Health points
1 - no response	≥75	6			
			Liver	Cirrhosis with portal hypertension. or encephalopathy	
Motor response			Cardiovascular	Class IV angina or at rest or with minimal self care activities	
6 - to verbal command			Pulmonary	Chronic hypoxemia or hypercapnia or polycythemia of pulmonary hypertension >40 mmHg	
5 - localizes to pain					
4 - withdraws to pain					
3 - flexion to pain					
2 - extension to pain					
1 - no response					
			Kidney	Chronic peritoneal or hemodialysis	
Verbal			Immune	Immune compromised host	
5 - oriented					
4 - confused					
3 - inappropriate words					
2 - incomprehensible sounds					
1 - no response					

Reference: Knaus et al., 1985[7]

10.7. Appendix 7: SOFA Score

Table 12. SOFA Score

Score	0	1	2	3	4
Nervous system					
Glasgow coma scale	15	13-14	10-12	6-9	<6
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 and mechanically ventilated	<100 and mechanically ventilated
Cardiovascular system	MAP ≥70	MAP <70	dopamine <5 µg/kg/min or dobutamine (any dose)	dopamine 5-15 µg/kg/min or norepinephrine ≤0.1 µg/kg/min or epinephrine ≤0.1 µg/kg/min	dopamine >15 µg/kg/min or norepinephrine >0.1 µg/kg/min or epinephrine >0.1 µg/kg/min
Liver					
bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Kidneys					
creatinine (mg/dL)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5.0
urine output (mL/day)				<500	<200
Coagulation					
Platelets ($10^3/\mu L$)	≥150	<150	<100	<50	<20
SOFA Score	**Sum of the 6 individual points=**				

Reference: Egi et al., 2020[8]

Table 13. qSOFA Criteria

Criteria
Altered mentation (GCS <15)
Respiratory rate ≥22 breaths/min
Systolic blood pressure ≤100 mmHg

Reference: Egi et al., 2020[8]

10.8. Appendix 8: Calculation of Estimated CrCL

Estimated CrCL will be calculated using the following Cockcroft-Gault formula[6]. The weight obtained at Screening should be used to qualify for entry into the study. In order to determine the need to adjust the dose and/or dosing interval of IV study intervention to be administered, the patient's estimated CrCL must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the patient's most recent actual (not ideal) body weight, and the Cockcroft-Gault formula.

Cockcroft-Gault formula:

Estimated CrCL is calculated by Cockcroft-Gault as follows:

1. For serum creatinine in mg/dL:
   estimated CrCL = [(140 – age) × weight in kilograms] /
   [72 × serum creatinine in mg/dL]
   [× 0.85 if female]

2. For serum creatinine in µmol/L:
   estimated CrCL = [(140 – age) × weight in kilograms × constant] /
   [serum creatinine in µmol/L]
   where constant = 1.23 for males and 1.04 for females

10.9. Appendix 9: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A-aDO_2	alveolar-arterial oxygen tension difference
ABG	arterial blood gas
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AMR	antimicrobial resistance
APACHE II	Acute Physiology and Chronic Health Evaluation II
APS	acute physiology score
AST	aspartate aminotransferase
AUC_{ss}	area under the plasma concentration curve at steady-state
$AUC_{ss,24}$	total daily area under the plasma concentration-time curve at steady-state
AVI	avibactam
β-hCG	beta-human chorionic gonadotropin
bpm	beats per minute
BUN	blood urea nitrogen
CAZ	ceftazidime
CD4	cluster of differentiation 4
CE	clinically evaluable
CFR	Code of Federal Regulations
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLSI	Clinical and Laboratory Standards Institute
CONSORT	Consolidated Standards of Reporting Trials
CrCL	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
$C_{ss,max}$	maximum plasma concentration at steady-state
CT	clinical trial
CTD	Common Technical Document
cUTI	complicated urinary tract infection
CV	coefficient of variation
DILI	drug-induced liver injury
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
eME	extended-microbiologically evaluable
EOT	End of Treatment
ESBL	extended-spectrum β-lactamase
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GGT	gamma-glutamyltransferase
HAP	hospital-acquired pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IP manual	investigational product manual
IRB	Institutional Review Board
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase-type β-lactamase
LFT	liver function test
LFU	late follow-up
MAP	mean arterial pressure
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MIC_{90}	minimum concentration to inhibit 90% of strains
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MTZ	metronidazole
N	number of patients in a group

Abbreviation	Term
N/A	not applicable
NIMP	noninvestigational medicinal product
OAT	organic anion transporter
PACL	Protocol Administrative Change Letter
PAH	p aminohippuric acid
PaO_2	partial pressure of oxygen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
PTA	probability of target attainment
q8h	every 8 hours
qSOFA	quick Sequential Organ Failure Assessment
qual	qualitative
RBC	red blood cell
ROW	rest of world
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOFA	Sequential Organ Failure Assessment
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TOC	test of cure
ULN	upper limit of normal
US	United States
VAP	ventilator associated pneumonia
WBC	white blood cell
WOCBP	woman of childbearing potential

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