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SYNOPSIS

Study Title: 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 Number: C3591036

Regulatory Agency or Public Disclosure Identifier Number: NCT04927312

Study Phase: 3

Name of Study Intervention: PF-06947386 (Ceftazidime-Avibactam)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: 1.0, 27 March 2023

Number of Study Center(s) and Investigator(s):

A total of 60 participants were enrolled at 27 sites in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not Applicable

Study Period:

The study initiation date was 01 October 2021 and the study completion date was 15 September 2022.

This study was neither discontinued nor interrupted.

Rationale:

PF-06947386 is a combination drug that contains ceftazidime, the third-generation cephalosporin antibiotic (β-lactam) and 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 Unites States (US) in February 2015 and in the European Union (EU) in June 2016. PF-06947386 is indicated in the US and Europe for the treatment of adults with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (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

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2020, it was approved for the treatment of bacteremia associated with, or suspected to be associated with, any of the above infections.

The pharmacokinetics (PK) of ceftazidime and avibactam is sufficiently similar across indications, and in Japanese, non-Japanese and non-Asian patient populations. Population PK modeling/simulation analysis has demonstrated sufficient exposure and high probability of target attainment 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 other countries. 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, extended-spectrum β-lactamases producing pathogens are increasing among the *Enterobacterales*, such as *Escherichia coli* (*E.coli*).

Hence, for the treatment of cIAI, broad-spectrum single agent (β-lactam/β-lactamase inhibitor combination drugs, carbapenems) or combination therapy regimens (concomitant use of cephem antibiotics) are recommended.

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Objectives, Endpoints, and Statistical Methods:

Table 1. Objectives and Endpoints

Type and Objective	Endpoints
Primary	
Efficacy	
To assess the efficacy of PF-06947386 plus metronidazole	Clinical response at the TOC visit
Secondary	
Efficacy	
To determine the efficacy of PF-06947386 plus metronidazole	Clinical response at EOT and LFU visits
To determine the per-patient microbiological response of PF-06947386 plus metronidazole	Per-patient microbiological response at EOT, TOC, and LFU visits
To determine the per-pathogen microbiological response of PF-06947386 plus metronidazole	Per-pathogen microbiological response at EOT, TOC, and LFU visits Per-pathogen microbiological response at EOT, TOC, and LFU visits by MIC categories
Safety	
To evaluate the safety and tolerability profile of PF-06947386 plus metronidazole in the treatment of participants with cIAIs	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
PK	
To evaluate the pharmacokinetics of the individual components of PF-06947386 in participants with cIAIs	Ceftazidime and avibactam plasma concentrations by nominal sampling window
Efficacy and safety	
To investigate safety and efficacy for participants with sepsis (if available)	Selected efficacy and safety endpoints as described above

AE = adverse event, cIAI = complicated intra-abdominal infection, CRP = C-reactive protein, EOT = end of treatment, IV = intravenous, LFU = late follow-up, MIC = minimum inhibitory concentration, SAE = serious adverse event, TOC = test of cure, WBC = white blood cell

Statistical Methods

No formal hypothesis testing was conducted. As an efficacy evaluation criterion, it was confirmed that the point estimate of proportion of patients with clinical cure at TOC visit in the clinically evaluable (CE) analysis set (the primary analysis) was ≥78.0%.

Main analysis of the primary endpoint included number of participants, frequency, and proportion and the 95% CI was calculated for the CE at TOC analysis set. The assessment by the adjudication committee was used.

Descriptive summaries were provided where appropriate for each of the primary and secondary endpoints. In general, summaries were presented for the modified intent-to-treat

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(MITT) and microbiologically modified intent-to-treat (mMITT) analysis sets, and the microbiologically evaluable (ME), extended microbiologically evaluable (eME), and CE analysis sets at the appropriate visit.

Methodology:

Study C3591036 assessed the efficacy and safety of PF-06947386 in Japanese patients with cIAI requiring hospitalization. This was a multicenter, open-label, single-arm study. The study had a maximum duration of approximately 6 weeks for each participant. This included 5 to 14 days of IV study period, TOC visit at Day 28, and LFU visit at Day 42.

Number of Participants (planned and analyzed):

Approximately 60 participants were planned to be enrolled to study intervention, which could contribute to have approximately 50 evaluable participants in the CE analysis set and 3 to 5 enrolled participants to meet the definition of the sepsis patients subset.

A total of 60 participants were enrolled to study intervention including 40 participants in the CE at TOC analysis set and 2 participants in the sepsis patients subset.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants ≥20 years at the time of the Screening visit with clinical evidence of cIAI, willing and able to give signed informed consent and meet all inclusion criteria and no exclusion criteria were enrolled in the study.

Clinical evidence of cIAI for pre-operative participants included requirement for surgical intervention, evidence of systemic inflammatory response, physical and/or imaging findings consistent with cIAI.

Criteria for intra-operative/post-operative participants included diagnosis of at least one of the following during 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.

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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 was extension beyond the organ with evidence of intraperitoneal involvement).

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

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	Concomitant
IMP or NIMP	IMP	IMP
Manufacturing Lot Number	21-AE-00133	21-AE-00151
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention was provided in vials. Each vial was labeled as required per country requirement.	Study intervention was provided in vials. Each vial was labeled as required per country requirement.

IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

Duration of Study Intervention:

Eligible participants with creatinine clearance (CL_{cr}) >50 mL/min were 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 to 14 days. For participants enrolled into the study whose CL_{cr} dropped to ≤50 mL/min while on IV investigational drug therapy, dosage adjustment was required depending on the degree of renal impairment based on the CL_{cr} value. All eligible participants received metronidazole (0.5 g) intravenously with an infusion duration of 60 minutes. When both PF-06947386 and metronidazole were administered at the same time, metronidazole was administered immediately after administration of PF-06947386.

Summary of Results:

Demographic and Other Baseline Characteristics:

In the MITT analysis set, all participants enrolled in the study were Asian. A slightly higher proportion of male participants (57.6%) versus female participants (42.4%) was included. The mean age was 57 years (range: 20 to 90 years). Distribution of participants was balanced across age categories and included 18.6% of participants over ≥75 years of age.

In the MITT analysis set, all participants had a primary diagnosis of cIAI. The most common secondary diagnoses were secondary peritonitis (100%), intra-abdominal abscess (72.9%), and perforated appendicitis (44.1%). Majority of the participants had polymicrobial infections (61.0%) versus monomicrobial infection (10.2%).

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Exposure:

Overall, the mean (SD) duration of treatment was 7.2 (2.19) days. Majority of the participants (54 [90.0%]) received treatment between 5 and 10 days.

Efficacy Results:

- Primary Efficacy Endpoint: Clinical Response at the TOC Visit
    - The proportion of participants in the CE analysis set with clinical cure at the TOC visit was 90.0% (95% CI: 76.3, 97.2), which was greater than the pre-specified point estimate threshold value of 78.0%.
    - The proportion of participants with clinical cure at the TOC visit was 90.0%, 88.1%, 85.7%, 94.3%, and 94.4% for the CE, MITT, mMITT, ME, and eME analysis sets, respectively.
- Secondary Efficacy Endpoint: Clinical Response at EOT and LFU Visits
    - The proportion of participants with clinical cure at the EOT visit was 90.5%, 91.5%, 90.5%, 94.4% and 94.6% for the CE, MITT, mMITT, ME, and eME analysis sets, respectively.
    - The proportion of participants with clinical cure at the LFU visit was 90.0%, 88.1%, 85.7%, 94.3% and 94.4% for the CE, MITT, mMITT, ME, and eME analysis sets, respectively.
    - Two (2) participants were included in the sepsis patients subset and achieved clinical cure at the TOC, EOT and LFU visits. Out of 2 participants, one (1) participant was included in the sepsis evaluable patients subset and achieved clinical cure at the TOC, EOT, and LFU visits. No clinical failures were observed in these subsets.
- Secondary Efficacy Endpoint: Per-patient Microbiological Response at EOT, TOC, and LFU Visits
    - In the mMITT analysis set, the proportion of participants with a favorable per-patient microbiological response was high (≥90.0%) and was similar at the TOC, EOT, and LFU visits. In the ME and eME analysis sets, the proportions of participants with a favorable per-patient microbiological response at each scheduled assessment were similar to those observed in the mMITT analysis set at the TOC, EOT, and LFU visits.
    - Both participants included in the sepsis patients subset (100.0%) and the single participant included in the sepsis evaluable patients subset (100.0%) had a favorable per-patient microbiological response at the TOC, EOT, and LFU visits.

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- Secondary Efficacy Endpoint: Per-pathogen Microbiological Response at EOT, TOC, and LFU Visits

    - The favorable per-pathogen microbiological response rate for Gram-negative pathogens (other than *R. planticola*), including *E. coli*, *K. pneumoniae*, *P. aeruginosa* were over 90% at all visits in the mMITT analysis set.

    - Per-pathogen microbiological response for eME and ME were similar to those observed for the mMITT analysis set at EOT, TOC, and LFU visits.

- Secondary Efficacy Endpoint: Per-pathogen Microbiological Response at EOT, TOC, and LFU Visits by MIC Categories

    - All *Enterobacterales* including *E. coli, K. pneumoniae*, and *P. aeruginosa* were susceptible. The favorable response rates for these pathogens other than *R. planticola* were over 90% at EOT, TOC, and LFU visits in the mMITT, eME, and ME analysis sets.

Safety Results:

A total of 112 AEs were reported for 42 (70.0%) participants overall. Number of participants who discontinued from the study due to adverse events (AEs) were 2 (3.3%). Participants with dose reduced or temporary discontinuation due to AEs were 3 (5.0%).

- Most of the AEs were mild or moderate in severity and only 1 AE was severe (pneumonia aspiration) with outcome of death, which was considered unrelated to the study drug.

- A total of 6 serious adverse events (SAEs) were reported for 3 participants overall. Of the 6 SAEs, 4 were reported in a single participant (pneumonia aspiration, contusion, ileus, and femur fracture). Another 2 participants had 1 SAE reported each, pyelonephritis and gout, respectively.

- Overall, 2 (3.3%) participants discontinued from the study (1 due to pneumonia aspiration and 1 due to pyelonephritis). Both of these events were not considered related to the study drug.

The most common laboratory test abnormalities were C-reactive protein (>1.1x ULN) in 60 (100.0%), albumin (<0.8x LLN) in 53 (88.3%) participants and lymphocytes/leukocytes (<0.8x LLN) in 48 (80.0%) participants. Three (3) (5.0%) and 5 (8.3%) participants reported abnormal ALT levels (>3.0x ULN) and AST levels (>3.0x ULN), respectively. Though 1 participant met the Hy's Law criteria, the investigator considered that this was not a Hy's Law case.

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No meaningful findings in the vital sign measurements or other observations related to safety were observed in this study.

Pharmacokinetic Results:

- All the participants in the PK Analysis Set obtained 3 PK samples on Day 3 or Day 4 of the study as planned. Plasma concentration of ceftazidime and avibactam were the highest around the end of infusion (anytime from 15 minutes prior to stopping until 15 minutes after stopping PF-06947386 infusion).

- Plasma concentration of ceftazidime and avibactam gradually decreased at time windows between 30 and 90 minutes and between 300 minutes and 360 minutes after stopping PF-06947386 infusion but before the next dose.

Conclusions:

- The proportion of participants in the CE analysis set with clinical cure at the TOC visit was 90.0%; (95% CI: 76.3 to 97.2), which was greater than the pre-specified point estimate threshold value of 78%.

- The clinical cure rates at the EOT and LFU visits were similar to the results at the TOC in the CE analysis set.

- The favorable per-patient microbiological response at all visits were similar to the result of clinical responses.

- All *Enterobacterales* including *E. coli* and *K. pneumoniae*, and *P. aeruginosa* were susceptible. The favorable response rates for these pathogens other than *R. planticola* were over 90% at EOT, TOC, and LFU visits in the mMITT, eME, and ME analysis sets.

- PF-06947386 was well tolerated, with no new safety signals identified in this Japanese study.

- For both sepsis patients subset (2 participants) and sepsis evaluable patients (1 participant), the clinical responses and microbiological responses observed for all participants were cure and favorable at EOT, TOC, and LFU visits, and no additional safety concerns were observed.