NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1

Title: A Real-World Observational Study of Zavicefta® (CAZ-AVI) to Describe the Effectiveness, Safety and Treatment Patterns Among Patients Infected With Complicated Intra-Abdominal Infections (cIAI) in China

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Rationale and background: CAZ-AVI was approved by the National Medical Products Administration (NMPA) on 21 May 2019 in China. Indications for adults approved include cIAI, hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

Research question and objectives: To meet Center for Drug Evaluation (CDE)'s requirement of observing the effectiveness and safety of CAZ-AVI after authorization, this study aims to retrospectively describe the effectiveness, safety and treatment patterns of CAZ-AVI for the treatment of cIAI based on hospital databases in a real-world clinical practice setting.

Study design: A Multi-center, retrospective, observational database study.

Setting: In this retrospective study, data were extracted from EMR of six Grade-A Tertiary hospitals in China. This study collected data from 7 April, 2023, to 21 June,

2023. The data of patients collected for CAZ-AVI use was dated from 9 September , 2019, to 20 January, 2023.

Subjects and study size, including dropouts:

The inclusion criteria for this study were as follows: patients who underwent a source control procedure and were diagnosed with cIAI prior to or during the procedure, patients who were treated with CAZ-AVI for cIAI during their hospital stay, and patients who were 18 years of age or older when they received the first dose of CAZ-AVI for the treatment of cIAI. Exclusion criteria were as follows: patients who had documentation of having received CAZ-AVI within 3 months before the index date (date of the first dose of CAZ-AVI for the cIAI), patients who participated in a clinical trial during their hospitalization for cIAI, and patients who were found to have cIAI caused by a Gram-negative species not expected to respond to CAZ-AVI (e.g., Acinetobacter spp., Stenotrophomonas spp., or bacteria producing Metallo-β-lactamases [MBL]) and without other Gram-negative pathogens.
No formal hypothesis testing was conducted for this study, and no power calculation was carried out to assess the number of patients needed. Based on a feasibility assessment, at least 180 patients were included in the study to provide reasonable precision for estimating the clinical cure rate and about an 80% probability of observing AEs with a low incidence rate of 1%. It was assumed that 75% of the included patients were exposed to CAZ-AVI treatment for at least 72 hours and were evaluable for clinical response.

Variables and data sources:
Research data was collected from the electronic medical record (EMR), hospital information system (HIS) and laboratory information system (LIS) of several hospitals in China. Baseline data included patient sociodemographic characteristics, clinical and treatment characteristics. Effectiveness, safety and treatment patterns were assessed in this study. Evaluation of effectiveness in terms of clinical response and in-hospital mortality was performed in patients with at least 72 hours of exposure to CAZ-AVI. Treatment patterns and safety were evaluated in all eligible patients exposed to at least one dose of CAZ-AVI. The clinical response at the end of treatment (EOT) of CAZ-AVI was abstracted from the EMR data. The treatment patterns and safety variables were abstracted from index date to the end of the current hospital stay.

Results: A total of 169 cIAI patients were eligible for analysis of the total 180 enrolled. Of the eligible patients, 144 patients were exposed to CAZ-AVI for at least 72 hours, and were included in the effectiveness analysis set (EAS).

In the full analysis set/safety analysis set (FAS/SAS) which included 169 patients, the mean (standard deviation [SD]) age of patients was 54.5 (14.82) years. The majority of patients were male (n=120, 71.0%). The median BMI was 22.95 kg/m^2.

147 (87.0%) patients in the SAS had cIAI related primary disease, and pancreatitis was the most common cIAI related primary disease, accounting for 55.0% in the SAS. The mean (SD) duration of infection before CAZ-AVI treatment was 28.5 (26.60) days in SAS. 117 (69.2%) of patients in the SAS were with liver injury which was defined as AST/ALT >3 ULN or TBIL >2 ULN with laboratory test at baseline.

In the SAS, sepsis (n=51, 30.2%) was the most common comorbidity. 68 (40.2%) patients in the SAS were immunocompromised, mostly due to transplantation and continuous glucocorticoid or immunosuppressant therapy. Respiratory support was used in 91 (53.8%) patients in SAS, and vasoactive agents were used in 89 (52.7%) patients in SAS, in which norepinephrine accounted for the highest proportion. 109 (64.5%) patients in SAS had polymicrobial results. *Klebsiella pneumoniae* (n=112, 66.3%) was the most common pathogen, followed by *Pseudomonas aeruginosa* (n=48, 28.4%)*, and Acinetobacter baumannii* (n=44, 26.0%).

For the effectiveness assessment, among the 144 patients in the EAS, 44.4% (95% CI: 36.3% to 52.6%) of them were assessed to be clinically cured. The effectiveness results varied among subgroups as anticipated: patients without liver injury (61.2% [95%CI: 47.6% to 74.9%]) and those who did not use vasoactive agent (56.9% [95%CI: 45.5% to 68.4%]) appeared to have higher clinical cure rates; while patients with CrCL ≤30 ml/min (16.7% [95%CI: 0.0% to 46.5%), liver injury (35.1% [95%CI: 25.5% to 44.8%]) and those who used vasoactive agent (31.9% [95%CI: 21.2% to 42.7%]) appeared to have lower clinical cure rates.

In regard to treatment patterns, CAZ-AVI was usually used as a salvage anti-infection therapy: 95.9% patients received prior antibiotics, with Carbapenems (84.6%) being the most common prior antibiotics, followed by tetracycline (tigecycline) (62.7%) and polymyxin (50.3%). The majority of the patients (95.9%) received CAZ-AVI in combination with other antibiotics. There were 24.3% patients received repeated CAZ-AVI treatment courses. Among patients who received single course uninterrupted treatment with CAZ-AVI (75.7%), the median treatment duration was 7.45 [range: 3.85 to 14.40] days, with 43.8% of them received CAZ-AVI for 5-14 days.

For the safety assessment, in-hospital all-cause mortality was 24.3% (41/169) among the 169 patients in the SAS, 1.2% (2/169) of the patients in the SAS had AEs with explicit attribution to CAZ-AVI. There was 1 (0.6%) patient with SAEs attributed to CAZ-AVI. No patient used CAZ-AVI in specific scenarios.

Discussion: This study showed the real-world clinical benefits of CAZ-AVI for the treatment of severe, often last resort (salvage) therapy of cIAI patients in a tertiary hospital setting across various provinces in China, confirming effectiveness of CAZ-AVI as evidenced by the analysis of clinical cure rate, in-hospital mortality, as well as providing treatment patterns and safety information.

Marketing Authorization Holder(s): Pfizer Ireland Pharmaceuticals Operations Support Group, Ringaskiddy, County Cork, Ireland

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