EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2018
EMA/PRAC/595509/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zavicefta

ceftazidime / avibactam

Procedure no: EMEA/H/C/004027/P46/003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

Procedure No. EMEA/H/C/004027/P46/003

Invented name: Zavicefta

International non-proprietary name: ceftazidime / avibactam

Marketing authorisation holder (MAH): Pfizer Ireland Pharmaceuticals

This application is in the area of: Clinical

eCTD sequences related to the procedure: 0031

1. Introduction

ZAVICEFTA® (CAZ-AVI ceftazidime/avibactam) is approved for use in Europe for the treatment of adults with cIAI, cUTI including pyelonephritis, hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), and infections due to aerobic Gram-negative organisms in patients with limited treatment options. As part of the agreed PIP, the applicant has conducted a single-blind, randomised, multi-centre, active controlled, study to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of ceftazidime and avibactam compared with cefepime in children from 3 months to <18 years of age with complicated urinary tract infections (cUTIs).

In this submission, the MAH presents a summary of the final data for paediatric Study C3591005 in line with the requirements of Article 46 Regulation (EC) No. 1901/2006. The results from this study have not raised any additional safety concerns. The available information is proposed to be added to the SmPC.

CAZ-AVI is currently available as an intravenous formulation supplied in a single vial (powder concentrate for solution for infusion 2000 mg/500 mg). The pharmaceutical formulation of CAZ-AVI used in this study was identical to that currently approved. No new biopharmaceutical data were generated during this application and no additional formulation development studies are currently planned.

The benefit-risk balance of Zavicefta remains positive.

2. Clinical Safety aspects

2.1. Study C3591005

Study C3591005 was initially sponsored by AstraZeneca. Sponsorship for this study was transferred to Pfizer, Inc, on 18 Sept 2017. The study was conducted by investigators contracted by and under the direction of the Sponsor. Data management, data analysis, and biostatistics were performed by PRA Health Sciences. The PRA Datalabs system was used for data collection and query handling. The PRA Drug Safety Department was responsible for collection of Serious Adverse Event (SAE) data, sending expedited SAEs safety reports, and timely reporting of SAEs to AstraZeneca.

Study Initiation and Completion Dates: 24 September 2015 and 15 September 2017.

Report Date: 01 May 2018

Phase of Development: Phase 2

Study sites: 25 centres spread globally

Study Objectives:

Primary Objective:

- To evaluate the safety and tolerability of ceftazidime and avibactam (CAZ-AVI) given at the selected dose regimen versus cefepime in paediatric patients aged $\geq$3 months to <18 years with complicated urinary tract infections (cUTI).

Secondary Objectives:

- To evaluate the descriptive efficacy of CAZ-AVI versus cefepime in paediatric patients aged ≥3 months to <18 years with cUTI.
- To evaluate the pharmacokinetics (PK) of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cUTI.

Study Design

This was a single-blind, randomised, multi-centre, and actively controlled trial conducted in hospitalised paediatric patients diagnosed with cUTIs requiring treatment with intravenous (IV) antibiotics. Patients aged from 3 months to <18 years with cUTI were randomised in a 3:1 ratio to receive CAZ-AVI or cefepime. Patients aged from 3 months to <1 year were to have been born at term (defined as gestational age >37 weeks). Patients were allocated to 1 of 4 cohorts based on age (Cohort 1: patients aged from 12 years to <18 years; Cohort 2: patients aged from 6 years to <12 years; Cohort 3: patients aged from 2 years to <6 years; Cohort 4: patients aged from 3 months to <2 years). Patients received IV treatment for a minimum of 72 hours (3 full days, ie, 9 doses if given 3 times daily, or 6 doses if given twice daily) before having the option to switch to an oral therapy on Day 4. The decision to switch to oral therapy was entirely at the Investigator's discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food. The total period of treatment (ie, IV drug and oral switch treatment) was to be between 7 and 14 days. Patients could have remained on IV study treatment up to Day 14.

Diagnosis and Main Criteria for Inclusion

Patients were to have been ≥ 3 calendar months to <18 years of age (patients aged ≥ 3 calendar months to <1 year must have been born at term [defined as gestational age ≥ 37 weeks]) with a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the Investigator to
be serious and required the patient to be hospitalised for treatment with IV therapy. For females of childbearing potential, negative serum pregnancy test was required at Screening.

Selection of Doses in the Study

The dosing regimens for CAZ-AVI in this study were selected based on safety and PK data in paediatric patients from Study D4280C00014, and predicted exposures from population PK models for ceftazidime and avibactam. Population PK models previously developed using data from Phase 1, 2, and 3 studies in adults (healthy subjects and patients with cIAI and cUTI) were updated with paediatric PK data from study D4280C00014. The updated models were then used to simulate a range of dose regimens to assess steady-state exposure measures (maximum plasma drug concentration [Cmax], area under the plasma concentration versus time curve [AUC], percent of time that free drug concentrations are above the minimum inhibitory concentration (MIC) over a dose interval [%fT >MIC] for ceftazidime, and percent of time that free drug concentrations are above the threshold concentration over a dose interval [%fT >CT] for avibactam) in paediatric patients relative to adults. The selected paediatric dose regimens are predicted to give >90% probability of PK/pharmacodynamics (PD) target attainment for the same PK/PD target as for adults (50% fT>MIC of 8 mg/L for ceftazidime, and 50% fT>CT of 1.0 mg/L for avibactam). Furthermore, for each of the paediatric dose regimens, average ceftazidime and avibactam exposures (Cmax and AUC) were predicted to be broadly comparable with reference values in adults who receive the approved CAZ-AVI dose regimen (2000 mg ceftazidime plus 500 mg avibactam, every 8 hours, 120 minutes intravenous (IV) infusion), which has been shown to be effective in pivotal Phase 3 studies in adult patients with cIAI.

The CAZ-AVI dose regimens for the 4 cohorts were:

Table S1. CAZ-AVI Dose Regimens by Age, Weight and Creatinine Clearance

Cohort	Age Range	Body Weight	CAZ-AVI Dose CrCl ≥50 mL/min	CAZ-AVI Dose CrCl ≥30 to <50 mL/min
			CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)	
1	12 years to <18 years	≥40 kg	2000 mg CAZ / 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	12 years to <18 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
2	6 years to <12 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	6 years to <12 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
3	2 years to <6 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4a	1 year to <2 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	6 months to <1 year	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	3 months to <6 months	All	40 mg/kg CAZ/ 10 mg/kg AVI	20 mg/kg CAZ/ 5 mg/kg AVI

CAZ-AVI= ceftazidime-avibactam; CrCl=creatinine clearance.

Study Treatment

Patients received IV treatment for a minimum of 72 hours (3 full days, ie, 9 doses if given 3 times daily, or 6 doses if given twice daily). Doses were based on the age and weight of the patient with adjustment for renal function. Beginning on Day 4, there was an option to switch to oral therapy at the Investigator's discretion. Patients could also continue to take IV CAZ-AVI or cefepime from Day 4 up to Day 14.

Efficacy Evaluations

Efficacy evaluations were secondary objectives of the study with an objective to evaluate the descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem. The (secondary) efficacy outcome measures were:

- Clinical response at End of 72 hours' treatment, End of Intravenous Treatment (EOIV), End of Treatment (EOT), and Test of Cure (TOC)
- Microbiological response at EOIV, EOT, TOC, and Late Follow-up (LFU)
- Clinical relapse at LFU
- Emergent infections

Pharmacokinetic Evaluations

PK blood samples were collected anytime on Day 3 within 15 minutes prior to or after stopping CAZ AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ AVI infusion. Plasma samples were analysed for CAZ-AVI concentrations using a validated, sensitive and specific method involving protein precipitation followed by specific high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) detection.

Safety Evaluations

Safety evaluations included adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), physical examination, and laboratory safety tests.

Statistical Methods:

Efficacy

The efficacy analysis of data in this study was based on 4 analysis sets of patients (intent-to-treat [ITT], microbiological ITT [micro-ITT], clinically evaluable [CE], and microbiologically evaluable [ME] analysis sets). Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) were provided for continuous variables, and counts and percentages with accompanying two sided 95% confidence intervals (CIs) (computed using Jeffrey's method) were presented for categorical variables.

The study was not powered for inferential testing and based on the 3:1 randomisation, direct comparisons of safety and efficacy data between treatment groups must be interpreted with caution.

Pharmacokinetics

CAZ-AVI plasma concentrations were summarised by descriptive statistics (number, mean, SD, minimum, median, maximum, geometric mean, and coefficient of variation).

Safety

No inferential statistical tests were performed for any safety parameters. All data were presented by treatment group, cohort, and overall for each treatment. Descriptive statistics (number, mean, SD, median, minimum, and maximum) were provided for continuous variables, and counts and percentages were presented for categorical variables. Safety analyses were conducted with the safety analysis set, with confirmatory analyses being performed with the safety evaluable analysis set.

RESULTS

Table S3. Patient Disposition

	CAZ-AVI (N=68)	CEF (N=29)	Total (N=101)
	n (%)	n (%)	n (%)
Patients randomised	68	29	97 (96.0)
Patients who were not randomised			4 (4.0)
Patients who received IV study treatment	67 (98.5)	28 (96.6)	95 (97.9)
Patients who were randomised but did not receive IV study treatment	1 (1.5)	1 (3.4)	2 (2.1)
Patients who completed the study up to the TOC visit	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed the study up to the LFU visit	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed IV study treatment	63 (92.6)	25 (86.2)	88 (90.7)
Patients who discontinued IV study treatment	4 (5.9)	3 (10.3)	7 (7.2)
Patient/parent/legal representative decision	1 (1.5)	0	1 (1.0)
Adverse event	3 (4.4)	0	3 (3.1)
Condition under investigation improved/patient recovered	0	1 (3.4)	1 (1.0)
Based on enrolment culture or susceptibility results	0	2 (6.9)	2 (2.1)
Patients who completed study	64 (94.1)	26 (89.7)	90 (92.8)
Patients prematurely withdrawn from study	4 (5.9)	3 (10.3)	7 (7.2)
Parent/Guardian decision	2 (2.9)	0	2 (2.1)
Lack of therapeutic response	0	1 (3.4)	1 (1.0)
Patient lost to follow-up	1 (1.5)	1 (3.4)	2 (2.1)
Other	1 (1.5)	1 (3.4)	2 (2.1)

Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the

The median age was 4.22 years (range: 0.3 to 17.7 years) in the CAZ-AVI group and 3.20 years (range: 0.3 to 17.9 years) in the cefepime group. For cohort 4, the median age was 11.4 months (range: 3.5 to 22.4 months) in the CAZ-AVI group and 9.5 months (range: 3.1 to 22.5 months) in the cefepime group. The majority of patients in the study were female in both groups (56/67 [83.6%] in the CAZ-AVI group and 21/28 [75.0%] in the cefepime group). Most (72 [75.8%]) of the patients were White. The distribution of racial origin reflects the countries that participated in the study. Seventeen (17 [17.9%]) patients were Asian, 1 (1.1%) patient was American Indian or Alaska Native, and 5 (5.3%) patients were classified of being of “Other” race.

Efficacy Results

Clinical Response

In general, across all analysis sets, favourable clinical response rates of >86% were observed at the End of 72 hour visit and were sustained through to the EOT visit, with responses remaining >80% at LFU for both treatment groups for the ITT, micro-ITT, and CE at LFU analysis sets. The clinical response rates in the individual cohorts were consistent with those observed in the overall study population; there were no notable trends observed within the cohorts in terms of clinical response in any of the analysis sets.

Clinical Relapse at LFU

A total of 4 (5.9%) patients were reported to have clinical relapse in the CAZ-AVI group in the ITT and 4 (7.4%) patients in the micro-ITT analysis sets. This number was 3 patients (6.8%) in the CE analysis set and 2 (12.5%) patients in the ME analysis set. No patients had clinical relapse at LFU in the cefepime group in any of the four efficacy analysis sets.

Clinical Response by Pyelonephritis Diagnosis at Screening

In the ITT population, at TOC, in the pyelonephritis sub-group, 49/55 patients (89.1%) in the CAZ-AVI group and 21/25 patients (84.0%) in the cefepime group had a favourable clinical response. Similar results were observed at each study visit. Overall, this sub-group analysis by pyelonephritis diagnosis was consistent with the overall clinical response.

Clinical Response at Test of Cure by Baseline Pathogen

In the micro-ITT analysis set, favourable clinical responses by pathogen at TOC for infections due to E. coli was 87.8% for the CAZ-AVI group and 81.8% for the cefepime group). There were 2 patients in the CAZ-AVI group infected with ceftazidime nonsusceptible (CAZ-NS) E. coli. One of these patients had favourable clinical responses at all time points and the other patient had favourable clinical responses at all time points except for the EOT visit, at which the response was indeterminate. The 1 patient in the cefepime group that was infected with CAZ-NS E. coli, had an isolate that was also resistant to cefepime at baseline and was a clinical failure.

The results for the ME analysis set were similar to the results for the micro-ITT population; most patients had favorable clinical responses by pathogen at TOC for infections due to E. coli (91.9% for the CAZ-AVI group and 86.7% for the cefepime group).

Per-Patient Microbiological Response

In the micro-ITT analysis set, favourable microbiological response rates of >60.9% were observed at the EOIV, EOT, and TOC visits for both treatment groups. Favourable microbiological response rate were lower at the LFU visit for both treatment groups than at the preceding visits (CAZ-AVI: 29.6%; cefepime: 17.4%). This was primarily due to a high percentage of indeterminate responses (ie, source specimen was not available to culture) at the LFU visit (CAZ-AVI: n = 32 [59.3%]; cefepime: n = 14 [60.9%]). As the LFU visit could have been performed via telephone, a urine culture was not required at this visit and therefore was not collected in a large proportion of patients for this reason. For the ME analysis set, the LFU favourable response rate was 62.5% for the CAZ-AVI group and 44.4% for the cefepime group. The favourable response rate results for the ME analysis set were different from the micro-ITT analysis set as data from patients with indeterminate responses were not included. The lower favourable response at LFU could also be partly attributed to the fact the visit could have been performed via telephone for any patient who had not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC, therefore microbiological culture results at LFU were primarily obtained from patients who may have been more unwell. There was nothing notable observed across cohorts in terms of microbiological response.

Per Pathogen Favourable Microbiological Response Rate at TOC by Pathogen

Across both treatment groups, favourable microbiological response rates for the CAZ-AVI and cefepime groups for E. coli at TOC were: 79.6% and 59.1% respectively in the micro-ITT analysis set and 86.5% and 66.7%, respectively in the ME analysis set.

Per Pathogen Favourable Microbiological Response Rate at TOC by Pathogen Group, Pathogen and Baseline Minimum Inhibitory Concentration (MIC)

Review of per-pathogen responses by MIC did not identify any trends. For the predominant pathogen (E. coli), there was no indication that increasing MIC was associated with a lower favourable response rate in either treatment group. The results for the ME analysis set mirrored those for the micro-ITT analysis set.

Persistence

There were 5 cases in each treatment (CAZ-AVI: 5/54 [9.3%] and cefepime: 5/23 [21.7%]) group at TOC of persistent Enterobacteriaceae infections. At LFU, there were 6/54 (11.1%) in the CAZ-AVI and

5/23 (21.7%) in the cefepime group. All patients who had a microbiological response of persistence (EOIV, EOT, TOC and/or LFU) in the micro-ITT analysis set had E. coli as a baseline pathogen.

Persistence with Increasing MIC

There were no reported cases of pathogens with reported persistence with increasing MIC in either treatment group.

Emergent Infections

A total of 3 patients (7.3%) had emergent infections in the CAZ-AVI group and there were none occurring in the cefepime group as assessed by the evaluability and clinical/microbiological assessment (ECMA) review committee. Of the 3 new infections, 2 patients were reported to have both underlying urological abnormalities and complicating factors.

Combined Response

A total of 43 (79.6%) patients in the CAZ-AVI group and 18 (78.3%) patients in the cefepime group and had a favourable combined response at EOIV. At TOC, 39 (72.2%) patients in the CAZ-AVI group and 14 (60.9%) patients in the cefepime group had a favourable combined response. Data for the ME population were consistent with that for the micro-ITT population.

Pharmacokinetic Results

Median plasma concentrations of CAZ and AVI were similar across age cohorts, although concentrations were lower for trough samples in Cohort 3 and lower for samples taken near the end of infusion in Cohort 4. Avibactam and ceftazidime PK parameters derived from population PK analysis and potential PK/pharmacodynamic (PD) relationships will be reported separately.

Safety Results

Of the 101 enrolled patients, 97 were randomised and 95 received treatment (67 were treated in the CAZ-AVI group and 28 were treated within in the cefepime group) and were included in the safety analysis set. The highest number of patients by age cohort was in Cohort 4 with 38 patients (CAZ-AVI n = 27 and cefepime n = 11) randomised. Cohort 1 randomised 19 patients (CAZ-AVI n = 13 and cefepime n = 6), Cohort 2 randomised 22 patients (CAZ-AVI n = 17 and cefepime n = 5), and Cohort 3 randomised 18 patients (CAZ-AVI n = 11 and cefepime n = 7).

For all cohorts combined, the median (minimum-maximum) duration of exposure to IV study drug was 4 (1 to 11) days for the CAZ-AVI group and 4 (2 to 11) days for the cefepime group. Greater than 90% of patients in both treatment groups were switched to oral therapy to complete their study treatment. The median duration of oral drug exposure was 7 days for patients in both treatment groups. The majority (84/95 [88.4%]) of patients in the study received 8 to 15 days of IV + oral therapy, consistent with the protocol recommended treatment duration of 7 to 14 days (IV + oral therapy combined).

The incidence of AEs in any category for each treatment for the safety analysis set is summarised below:

Table S4. Adverse Event in any Category (Safety Analysis Set)

Adverse event category	CAZ-AVI (N = 67) n (%)	CEF (N = 28) n (%)
Any AE	36 (53.7)	14 (50.0)
Any AE with outcome = death	0	0
Any SAE	8 (11.9)	2 (7.1)
Any AE leading to discontinuation of study treatment[a]	3 (4.5)	0
Any AE with severe intensity	6 (9.0)	2 (7.1)
Any AE of special interest	10 (14.9)	4 (14.3)
Any AE related to study IV treatment[b]	7 (10.4)	1 (3.6)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more

The most frequently reported system organ class (SOC) was infections and infestations. The most frequently reported AEs, by preferred term (PT), were Diarrhoea and urinary tract infection in the CAZ-AVI group, each in 5 patients (7.5%), and Diarrhoea in 3 patients (10.7%) in the cefepime group. In general, reported AEs were mild in intensity and considered not related to study treatment. Three (4.5%) patients in the CAZ-AVI group had AEs leading to permanent discontinuation of study treatment. Serious adverse events (SAEs) were experienced by 10 patients (8 [11.9%] in CAZ-AVI group and 2 [7.1%] in the cefepime group). Of these SAEs, only one was judged to be related to study treatment by the Blinded Observer (severe Nervous system disorder), which resolved and led to permanent discontinuation of study treatment. In terms of cephalosporin class effects and AEs of special interest (AEoSI), there were 10 (14.9%) patients with AEoSI reported during the study in the CAZ-AVI group, which were within the safety topics of liver disorders, diarrhoea, and hypersensitivity/anaphylaxis, none of which were considered to be SAEs. Notably, there were no AEoSI reported within the safety topics of haematological disorders and renal disorders and there were no reported cases of C. difficile. There were no deaths during the study. In general, there were no trends observed in changes from baseline for the majority of clinical laboratory tests with the exception of C-reactive protein (CRP) and leukocyte count; for both of these analytes, there was a trend for decreasing levels, consistent with recovery from infection.

For vital signs, temperature and heart rate decreased from elevated baseline values towards normal ranges throughout the study, consistent with recovery from infection. There were no other trends observed in changes from baseline for other vital signs, ECG, or physical examinations variables. No patients met potential Hy's Law criteria during the study.

Conclusion(s):

CAZ-AVI was generally well tolerated and appeared effective for the treatment of paediatric patients $\geq$3 months of age to <18 years of age with cUTI, including those with CAZ-NS strains. Overall, the findings from this study extend the previous determination of safety and efficacy for CAZ-AVI for the treatment of adult patients with cUTI to the paediatric population and no new safety concerns were identified.

2.2. Discussion

The applicant has submitted a study in the paediatric population; this study was part of the agreed PIP. The doses selected in the study were based on previously available data and PK modelling and simulation, however these reports were not available with the current submission and will be submitted separately.

The primary objective of this study was to evaluate the safety and tolerability of CAZ-AVI in paediatric patients. The safety results from this study suggest that CAZ-AVI was well tolerated. The sample size of this study was small and therefore the safety and tolerability conclusions should be interpreted with caution.

Based on the results of the present study, there do not appear to be any new safety concerns in the paediatric population. The applicant has proposed to add the available information in the SmPC at a later stage.

3. Changes to the Product Information

None proposed at present.