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Human Medicines 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/P46/004

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	25.04.2022	25.04.2022	☐
☐	CHMP Rapporteur Assessment Report	30.05.2022	31.05.2022	☐
☐	CHMP members comments	13.06.2022	13.06.2022	☐
☐	Updated CHMP Rapporteur Assessment Report	16.06.2022	16.06.2022	☐
☒	CHMP adoption of conclusions:	23.06.2022	23.06.2022	☐

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1. Introduction

On 23 March 2022, the MAH submitted the final Clinical Study Report for a paediatric study for Zavicefta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure(s) generated during the EU approval of the HAP/VAP indication in paediatric patients in September 2021 (EMEA/H/C/004027/II/0015).

A short critical expert overview has also been provided to provide information from a prematurely terminated (26 September 2021) study C3591025 titled "A Phase 1, Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months to Less Than 18 Years of Age Who are Hospitalized and Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia".

About the product

Zavicefta - Ceftazidime-avibactam (CAZ-AVI) - is a fixed dose combination (FDC) that has been developed as an IV administered compound for treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime.

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 paediatric patients (neonates to adolescents <18 years of age) 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.

Avibactam is a non-betalactam-lactamase inhibitor with a spectrum of beta-lactamases of class A and class C, including ESBLs and serine-based carbapenemases (KPCs). It also inhibits class D beta-lactamases (e.g. OXA-48 type KPC). Avibactam has no inhibitory effect on class B metallo-beta-lactamases.

The fixed dose combination of CAZ-AVI was approved for use in adults in the United States in 2015 with cIAI in combination with metronidazole, cUTI, or HAP/VAP), and for use in children 3 months of age and older (with cIAI in combination with metronidazole, or cUTI) in 2019, under the brand name AVYCAZ. Approval for use in adults in Europe was granted in 2016 under the brand name Zavicefta. Extension of indication has been approved in October 2020 to include paediatric patients aged 3 months to less than 18 years for Zavicefta (for the treatment of cIAI and cUTI, HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options).

Approved indication(s) and posology

Indication

Zavicefta is indicated in adults and paediatric patients aged 3 months and older for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology (of note; only the approved posology for the paediatric population is shown here):

It is recommended that Zavicefta should be used to treat infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section 4.4).

Posology

(…)

Dosage in paediatric patients with creatinine clearance (CrCL) > 50 mL/min/1.73 m²

Table 1 shows the recommended intravenous doses for paediatric patients with estimated creatinine clearance (CrCL) > 50 mL/min/1.73 m² (see sections 4.4 and 5.1).

Table 1 Recommended dose for paediatric patients with estimated CrCL1 > 50 mL/min/1.73 m²

Type of infection	Age group	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI[2,3] OR cUTI including pyelonephritis[3] OR HAP/VAP[3]	6 months to <18 years	50 mg/kg/12.5 mg/kg **to a maximum of** 2 g/0.5 g	Every 8 hours	2 hours	cIAI: 5 – 14 days cUTI[4]: 5 – 14 days HAP/VAP: 7 – 14 days
			Every 8 hours	2 hours	
OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[2,3]	3 months to <6 months[6]	40 mg/kg/10 mg/kg	Every 8 hours	2 hours	LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]

[1] CrCL estimated using the Schwartz bedside formula.
[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
[4] The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy.
[5] There is very limited experience with the use of Zavicefta for more than 14 days.
[6] There is limited experience with the use of Zavicefta in paediatric patients 3 months to < 6 months (see section 5.2).

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the paediatric study C3591025: *a Phase 1, Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months to Less Than 18 Years of Age Who are Hospitalized and Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia* has been part of a clinical development program for approval of the nosocomial pneumonia (NP) indication. The extension of indication to include the NP indication (including HAP/VAP) has, however, already been granted (EMEA/H/C/004027/II/0015). See additional information below.

According to the MAH the study was terminated 26th of September 2021 after regulatory consultations subsequent to the EU approval of the HAP/VAP indication in paediatric patients and because of slow enrolment. The applicant is now submitting the results collected in study C3591025 in accordance with Article 46 of Regulation (EC) No1901/2006, as requested.

2.2. Information on the pharmaceutical formulation used in the study

The MAH has not provided information regarding the pharmaceutical formulation used in the study, although the formulation approved in Europe is a fixed dose combination product; Vials contain the equivalent of 2 g ceftazidime and 0.5 g avibactam powder for concentrate for solution for infusion.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- the paediatric study C3591025: Phase 1, Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months to Less Than 18 Years of Age Who are Hospitalized and Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia.

2.3.2. Clinical study

Study C3591025: A Phase 1, Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months to Less Than 18 Years of Age Who are Hospitalized and Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia

Description

Methods

Study participants/sample size

This was a multicentre, multinational, open-label single-dose PK study. The study was planned to enrol approximately 32 participants at approximately 43 sites and 14 countries in the Americas, Europe, and Asia. The study aimed to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV infusion. The study outline is shown in Figure 1.

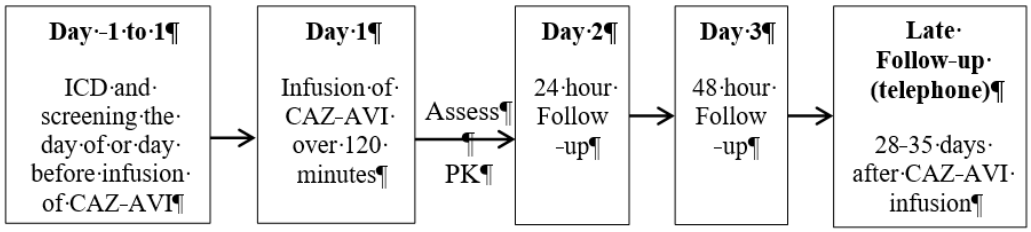

Figure 1 Study outline Source: Appendix 16.1.1, Protocol Section 3

Participants were hospitalized paediatric patients who were receiving systemic antibiotic therapy for suspected or confirmed NP, defined as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including VAP, defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation. Participants were planned to be enrolled in 4 cohorts of descending age, each consisting of at least 8 evaluable participants.

An evaluable participant was one who had received the complete single IV dose of CAZ-AVI and provided PK blood samples at ≥50% of the sampling time points. The definition of an evaluable participant was used for enrolment purposes only and did not impact the definition of the PK analysis set. Each participant received a single IV dose of CAZ-AVI administered as an intravenous infusion over a 120-minute period. Blood samples were collected from all participants at pre-specified timepoints after the infusion to evaluate the PK of ceftazidime and avibactam. Participants were followed for 48 hours after the end of the infusion.

Treatments

According to the MAH the single dose IV infusion of CAZ-AVI was based on age and weight of the participant, with adjustment according to renal function, as detailed in the study Protocol (see Table 2 below). The dosing regimen for CAZ-AVI in this study seems to be in accordance with the previously approved dosing regiments for the respective indication.

Table 2 CAZ-AVI Doses in Relationship to Age, Weight, and Renal Function. Source: Final study protocol C3591025 page 26.

Cohort	Age range	Body weight	CAZ-AVI dose CrCL ≥50 mL/min/1.73 m^2	CAZ-AVI dose CrCL ≥30 to <50 mL/min/1.73 m^2
1[a]	12 years to <18 years	≥40 kg	2000 mg CAZ 500 mg AVI	1000 mg CAZ 250 mg AVI
1[a]	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[a]	6 years to <12 years	≥40 kg	2000 mg CAZ 500 mg AVI	1000 mg CAZ 250 mg AVI
2[a]	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[a]	2 years to <6 years	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	1 year to <2 years	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	6 months to <1 year	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	3 months to <6 months	All	40 mg/kg CAZ 10 mg/kg AVI	20 mg/kg CAZ 5.0 mg/kg AVI

a. Subjects considered for entry into the study will be within the body mass index (BMI) range between the 5th percentile and ≤95th percentile according to height, weight, and age.
b. BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

Objectives

The following objectives and main endpoints were evaluated in paediatric patients from 3 months to less than 18 years of age who are hospitalized and receiving systemic antibiotic therapy for suspected or confirmed NP, including VAP.

Table 3 Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
PK (Study C3591025 CSR Section 11.1.1)	• To characterize the PK of a single intravenous dose of CAZ-AVI in paediatric participants aged 3 months to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed NP, including VAP.	• CAZ and AVI plasma concentrations by nominal time. • CAZ and AVI PK parameters calculated by NCA (Cohorts 1 and 2 only).
Secondary		
Safety (Study C3591025 CSR Section 12)	• To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in paediatric participants aged 3 months to less than 18 years with NP, including VAP.	• Safety and tolerability endpoints include AEs, SAEs, deaths, discontinuations due to AEs and laboratory abnormalities.
Exploratory (Not Reported)[a]		
ELF by BAL	• To determine CAZ-AVI concentrations in bronchial ELF by BAL from participants undergoing bronchoscopy for their clinical management if bronchoscopy is performed within the PK sampling interval after CAZ-AVI infusion.	• CAZ and AVI ELF:plasma concentration ratios.

Source: Study C3591025 Appendix 16.1.1, Protocol Section 2
a Exploratory PK results are not reported, as no participant had a bronchoscopy.

Outcomes/endpoints

See above under "Objectives".

Statistical Methods

Pharmacokinetic Evaluations: The PK analysis set consisted of all subjects who received a complete IV study dose of CAZ-AVI and had at least 1 ceftazidime and/or avibactam plasma measurement available. Blood samples for PK analyses (0.5 mL per sample) were to be obtained 2, 2.5, 3.5, 5, 8, 12, and 24 hours following the CAZ-AVI infusion for Cohort 1 (7 samples); 2, 2.25, 3, 4, 6, and 13 hours following the CAZ-AVI infusion for Cohort 2 (6 samples); and 2, 2.25, 4, and 6 hours following the CAZ-AVI for Cohorts 3 and 4 (4 samples). The following plasma PK parameters for ceftazidime and avibactam were calculated for each participant, as applicable, using NCA of plasma concentration-time data (see Table 4) (the participants in Cohorts 1 and 2 had 6-7 PK samples planned and were to be included in NCA, but the participants from Cohorts 3 and 4 only had 4 PK samples, so were not included in NCA). Samples below the lower limit of quantitation were set to zero for analysis. Actual sample collection times were used for the PK analysis.

Table 4 Pharmacokinetic Parameters Determined in Study C3591025

Parameter	Definition	Method of Determination
AUC_8	Area under the concentration-time profile from time zero to 8 hours post dose.	Linear/Log trapezoidal method
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the concentration-time profile from time zero extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{last}	Time of last quantifiable plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Loge(2)/k_{el}$, where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL [a]	Apparent oral clearance	$Dose / AUC_{inf}$
V_z [a]	Apparent volume of distribution	$Dose / (AUC_{inf} \times k_{el})$
V_{ss} [a]	Apparent volume of distribution at steady-state	CL × MRT, where MRT is mean residence time, calculated as: $[AUMC_{tau} + tau(AUC_{inf}-AUC_{tau})]/AUC_{tau}$ where $AUMC_{tau}$ is the area under the first moment curve derived using the linear/log trapezoidal method

a. If data permitted

The following supporting data from the estimation of t½ were also reported: the terminal phase rate constant (kel); the first, last, and number of time points used for the log-linear regression ($kel,_{t(lo)}$, $kel,_{t(hi)}$, and $kel,_{t(n)}$); the goodness-of-fit statistic from the regression (r^2); and the percent of the area under the plasma concentration-time curve from time zero to infinite time, AUC_{inf}, obtained by forward extrapolation ($AUC_{extrap\%}$). Unless otherwise noted, parameters marked "if data permit" were reported only where a well-characterized terminal phase was observed. A well-characterized terminal phase is defined as one with at least 3 data points, $r^2 \geq 0.9$, and $AUC_{extrap\% \leq 20}$.

Results

Recruitment/Number analysed

A total of 4 Asian male and female participants aged 1-9 years old receiving systemic antibiotic therapy for suspected or confirmed NP, defined as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including VAP, defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation received study

intervention, were enrolled. Of the enrolled participants one was in Cohort 2 (≥6 years to <12 years of age), one in Cohort 3 (≥2 years to <6 years of age), and two in Cohort 4 (≥3 months to <2 years of age). No participant was enrolled from Cohort 1. All participants completed the study.

Baseline data

Four participants were Asian.

All 4 participants were diagnosed with pneumonia, and time from primary diagnosis to the study treatment administration (duration since onset) ranged from 2 to 3 days. All included participants had normal renal function or mild renal impairment, defined as CrCl ≥50 mL/min/1.73m^2.

Pharmacokinetic results

All 4 enrolled participants were included in the PK analysis set. One participant enrolled from Cohort 2 had intensive PK collected and was included in the NCA using actual PK sampling times following a single dose administration of CAZ-AVI.

Individual CAZ and AVI concentration-time profiles following a single IV infusion were presented graphically on a semi-log scale using actual PK sample collection time. The plasma concentrations of CAZ and AVI were summarized by cohort using nominal PK sample collection time. Descriptive statistics such as mean, SD, minimum, median, maximum, geometric mean, and coefficient of variation are not available due to the limited number of participants. According to the MAH, the PK parameters of CAZ and AVI were supposed to be calculated by NCA using actual PK sampling times following a single dose administration of CAZ-AVI for Cohorts 1 and 2, although no participant was enrolled from Cohort 1.

Efficacy results

No efficacy data was collected in Study C3591025.

Safety results

No participant was enrolled from Cohort 1. All 4 participants received a single dose of CAZ-AVI as planned and all participants completed the study.

Incidence of Adverse Events

Up to 48 hours after the end of infusion, there were 3 TEAEs reported in 2 participants, both in Cohort 4; 1 had a hernia (deemed not treatment related) and pyrexia (treatment-related), and the other had a rash (treatment related). All 3 AEs were non-serious and mild.

Up to late follow-up (LFU), there were 15 TEAEs reported in 3 participants, (1 in Cohort 3, and 2 in Cohort 4). The reported TEAEs were pyrexia (in 2 patients), hernia, alanine aminotransferase (ALAT) increased, aspartate aminotransferase (ASAT) increased, brain natriuretic peptide (BNP) increased, protein urine present, hypoglycaemia, metabolic alkalosis, headache, urethral disorder, acute respiratory distress syndrome (ARDS), tonsillar hypertrophy, dermatitis diaper and rash in one patient each. All but one (ARDS which was severe and serious) were reported as mild in severity.

One of the TEAEs was an SAE of ARDS (assessed as not treatment-related by the investigator) in a participant in Cohort 4. The remaining 14 TEAEs were non-serious AEs and of mild severity, and all

were considered not related to treatment by the unblinded investigator, with the exception of 2 TEAEs (rash and pyrexia in two participants in Cohort 4) which were considered treatment-related.

Other Serious Adverse Events

Up to LFU, there was 1 SAE reported in this study, which occurred in 1 participant in Cohort 4 who had severe acute respiratory distress syndrome (classified as SAE). The event occurred during LFU (on Study Day 18) and was not considered related to the study intervention by the unblinded investigator, who assessed the event as due to disease under study.

No deaths or discontinuations from the study due to AEs were reported during the study. As this was a single-dose study, temporary discontinuations or dose reduction due to AEs were not applicable.

No laboratory data were considered clinically significant by the investigator. For one patient, however, laboratory measurements were not done, and hence, reported as protocol deviation.

Overall, there were no clinically significant findings in vital signs according to the MAH.

2.3.3. Discussion on clinical aspects

In the EU, Zavicefta is approved for paediatric patients (3 months to 17 years) with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis and hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options.

As mentioned above, the dose selection in paediatric patients with HAP/VAP and the approval of the paediatric indication was based on simulations only. At time of approval no PK data were available in paediatric patients with HAP/VAP. Hence extrapolation of efficacy to the paediatric HAP/VAP population was based on data from adult datasets across all 3 approved indications (cIAI, cUTI, and HAP/VAP) and PK data from paediatric patients with cUTI and cIAI.

The MAH submitted data from a paediatric study in accordance with Article 46 of Regulation (EC) No1901/2006.

The doses selected in the study were identical to the paediatric doses for Zavicefta as already approved in the EU.

The primary objective of the study was to characterize the PK of a single IV dose of CAZ-AVI in paediatric participants aged 3 months to less than 18 years who were receiving systemic antibiotic therapy for suspected or confirmed NP, including VAP. Since the current study is a single dose study it is not possible to make direct comparison to the simulated steady state exposures for HAP/VAP in the EMEA/H/C/004027/II/0015 procedure. Overall, no PK conclusions can be made at this time due to limited data. Of note, although not requested by the CHMP, the MAH states that the CAZ and AVI plasma concentration and paediatric patient demographic data from this study will be combined with the data from appropriate previous clinical studies in paediatric patients and/or adults for a population PK analysis and that the results of a population PK modelling and simulation analysis will be reported separately. This is appreciated, and further assessment awaits results from the updated population PK modelling.

Evaluation of safety and tolerability of a single IV dose of CAZ-AVI in paediatric participants aged 3 months to less than 18 years with NP, including VAP, was a secondary objective of the study.

Overall, there was 1 serious adverse event (SAE) in 1 participant (Cohort 4) and also reported as severe. This SAE occurred between 48 hours after the end of infusion and late follow-up (LFU). The SAE was not considered treatment related by the unblinded investigator.

There were 3 non-serious all-causality TEAE(s) reported in 2 participants in Cohort 4 up to 48 hours after the end of infusion, whereby 1 TEAE in each participant (pyrexia and rash, respectively) was considered as treatment-related by the unblinded investigator. Up to LFU, there were 15 TEAEs reported in 3 participants. All but one (ARDS which was severe) were reported as mild in severity.

No deaths or discontinuations from the study due to AEs were reported during the study.

There were no new or unexpected safety findings identified following a single intravenous dose of CAZ-AVI administered to 4 paediatric participants aged ranging from 1 year to 10 years with NP, including VAP. A single intravenous dose of CAZ-AVI was well tolerated in all patients enrolled, bearing in mind the very limited safety database (N=4).

3. Overall conclusion and recommendation

Although limited, the data provided in this submission are not considered to raise any safety or efficacy concerns for Zavicefta (ceftazidime/avibactam) in the paediatric population. Hence, the benefit/risk balance remains unchanged and positive in the approved indications at present.

No further action required, however additional modelling and simulation results are expected. The MAH states in the submitted application that the new CAZ and AVI data from this study will be combined with the data from appropriate previous clinical studies in paediatric patients and/or adults for a population PK analysis and that the results of a population PK modelling and simulation analysis will be reported separately.

☒ **PAM Fulfilled**