

Clinical trial results:

A Phase I Study to Assess the Pharmacokinetics, Safety and Tolerability of a Single Dose of Ceftazidime Avibactam (CAZ AVI) in Children From 3 Months of Age to <18 Years Who Are Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Infection Summary

EudraCT number	2013-001900-13	
Trial protocol	Outside EU/EEA	
Global end of trial date	09 October 2014	
Results information		
Result version number	v1 (current)	
This version publication date	01 February 2017	
First version publication date	08 May 2015	

Trial information

Trial identification		
Sponsor protocol code D4280C00014		
Additional study identifiers		
ISRCTN number	-	
ClinicalTrials.gov id (NCT number)	NCT01893346	
WHO universal trial number (UTN)	-	
N	-	

Notes:

Sponsors	
Sponsor organisation name	AstraZeneca Pharmaceuticals
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom, SK10 4TG
Public contact	Paul Newell, MBBS MRCP MFPM, AstraZeneca, paul.newell@astrazeneca.com
Scientific contact	Paul Newell, MBBS MRCP MFPM, AstraZeneca, paul.newell@astrazeneca.com

Notes:

Paediatric regulatory details		
Is trial part of an agreed paediatric investigation plan (PIP)	Yes	
EMA paediatric investigation plan number(s)	EMEA-001313-PIP01-12	
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No	

Notes:

Results analysis stage		
Analysis stage	Final	
Date of interim/final analysis	08 December 2014	
Is this the analysis of the primary completion data?	Yes	
Primary completion date	09 October 2014	
Global end of trial reached?	Yes	
Global end of trial date	09 October 2014	
Was the trial ended prematurely?	No	

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to characterize the pharmacokinetics of single dose CAZ AVI in a pediatric population.

Key PK parameters are shown for cohorts 1 and 2. For cohorts 3 and 4 (where children were <6 years of age), sparse sampling scheme was used for PK samples to limit the volume of blood required. PK parameters cannot be derived from these sparse PK samples without population PK analysis. Thus the PK is not described here, but will be reported in a separate population PK report.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The investigator at each center ensured that the patient, parent, guardian, or legal representative (as appropriate) was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. The patient, parent, guardian, or legal representative (as appropriate) were notified that they were free to discontinue from the study at any time and were given the opportunity to ask questions and allowed time to consider the information provided.

Background therapy:

Patients in the study were hospitalized pediatric patients receiving systemic antibiotic therapy for suspected or confirmed infection.

Evidence for comparator:

No comparator group

Actual start date of recruitment	26 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	32
EEA total number of subjects	0

Notes:

Subi	ects	enro	lled	ner	age	group
Jubi	CCLS		'IICU	DCI	auc	MI OUD

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	8
Children (2-11 years)	16
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 26 July 2013 Last patient last visit: 09 October 2014

Pre-assignment

Screening details:

Eligibility was determined by investigator, prior to enrollment. Patients were selected on the basis of the age requirements for the appropriate cohort and after obtaining written informed consent from the parent or legal guardian and assent from patients (as appropriate). Screening assessments were completed prior to study drug administration.

completed prior to study drug administration.				
Period 1				
Period 1 title	Overall Study (overall period)			
Is this the baseline period?	Yes			
Allocation method	Not applicable			
Blinding used	Not blinded			
Arms				
Are arms mutually exclusive?	Yes			
Arm title	Cohort 1 aged ≥12 to <18 years			
Arm description:				
aged ≥12 to <18 years				
Arm type	Experimental			
Investigational medicinal product name	Ceftazidime			
Investigational medicinal product code				
Other name				
Pharmaceutical forms	Powder and solution for solution for injection			
Routes of administration	Intravenous use			
Dosage and administration details:				
	combined infusion with avibactam over a 2 hour period. for ty the dose for both ceftazidime and avibactam was halved.			
Investigational medicinal product name	Avibactam			
Investigational medicinal product code				
Other name				
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion			
Routes of administration	Intravenous use			
Dosage and administration details:				
	mbined infusion with ceftazidime over a 2 hour period. for cy the dose for both ceftazidime and avibactam was halved.			
Arm title	Cohort 2 aged ≥6 to <12 years			
Arm description:	•			
aged ≥6 to <12 years				
Arm type	Experimental			
Investigational medicinal product name	Avibactam			
Investigational medicinal product code				
Other name				
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion			
Routes of administration	Intravenous use			

Dosage and administration details:			
500 mg (patients >=40kg) or 12.5 mg/kg (patients <40kg) avibactam administered as a combined infusion with ceftazidime over a 2 hour period. for patients with moderate renal insufficiency the dose for both ceftazidime and avibactam was halved.			
Investigational medicinal product name	Ceftazidime		
Investigational medicinal product code			
Other name			
Pharmaceutical forms	Powder and solution for solution for injection		
Routes of administration	Intravenous use		
Dosage and administration details:			
2000 mg (patients >=40kg) or 50 mg/kg (patients <40kg) ceftazidime administered as a combined infusion with avibactam over a 2 hour period. for patients with moderate renal insufficiency the dose for both ceftazidime and avibactam was halved			
Arm title	Cohort 3 aged ≥2 to <6 years		
Arm description:			
aged ≥2 to <6 years			
Arm type	Experimental		
Investigational medicinal product name	Avibactam		
Investigational medicinal product code			
Other name			
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion		
Routes of administration	Intravenous use		
Dosage and administration details:			
	a combined infusion with ceftazidime over a 2 hour period. for y the dose for both ceftazidime and avibactam was halved.		
Investigational medicinal product name	Ceftazidime		
Investigational medicinal product code			
Other name			
Pharmaceutical forms	Powder and solution for solution for injection		
Routes of administration	Intravenous use		
Dosage and administration details:			
50 mg/kg ceftazidime administered as a combined infusion with avibactam over a 2 hour period. for patients with moderate renal insufficiency the dose for both ceftazidime and avibactam was halved			
Arm title	Cohort 4 aged ≥3 months to <2 years		
Arm description:			
aged ≥3 months to <2 years			
Arm type	Experimental		
Investigational medicinal product name	Avibactam		
Investigational medicinal product code			
Other name			
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion		
Routes of administration	Intravenous use		
Dosage and administration details:			
12.5 mg/kg avibactam administered as a combined infusion with ceftazidime over a 2 hour period. for patients with moderate renal insufficiency the dose for both ceftazidime and avibactam was halved.			
Investigational medicinal product name	Ceftazidime		
Investigational medicinal product code			
Other name			
Pharmaceutical forms	Powder and solution for solution for injection		
Routes of administration	Intravenous use		
Dosage and administration details:			
50 mg/kg ceftazidime administered as a	combined infusion with avibactam over a 2 hour period. for		

Number of subjects in period 1	Cohort 1 aged ≥12 to <18 years	Cohort 2 aged ≥6 to <12 years	Cohort 3 aged ≥2 to <6 years
Started	8	8	8
Patients who received full infusion	8	8	8
Completed	8	7	8
Not completed	0	1	0
Lost to follow-up	-	1	-

Number of subjects in period 1	Cohort 4 aged ≥3 months to <2 years
Started	8
Patients who received full infusion	8
Completed	8
Not completed	0
Lost to follow-up	-

Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	1	3
Not Hispanic or Latino	8	7	5
Unknown or Not Reported	0	0	0

Cohort 4 agod > 2 Tatal					
Reporting group values	Cohort 4 aged ≥3 months to <2 years	Total			
Number of subjects	8	32			
Age categorical					
Units: Subjects					
In utero	0	0			
Preterm newborn infants (gestational age < 37 wks)	0	0			
Newborns (0-27 days)	0	0			
Infants and toddlers (28 days-23 months)	8	8			
Children (2-11 years)	0	16			
Adolescents (12-17 years)	0	8			
Adults (18-64 years)	0	0			
From 65-84 years	0	0			
85 years and over	0	0			
Age Continuous					
Units: years					
arithmetic mean	0.924				
standard deviation	± 0.5007	-			
Gender, Male/Female					
Units: participants					
Female	3	17			
Male	5	15			
Race (NIH/OMB)					
Units: Subjects					
American Indian or Alaska Native	0	1			
Asian	0	1			
Native Hawaiian or Other Pacific Islander	0	0			
Black or African American	3	6			
White	5	24			
More than one race	0	0			
Unknown or Not Reported	0	0			
Ethnicity (NIH/OMB)					
Units: Subjects					
Hispanic or Latino	1	5			
Not Hispanic or Latino	7	27			
Unknown or Not Reported	0	0			

End points

End points reporting groups	
Reporting group title	Cohort 1 aged ≥12 to <18 years
Reporting group description:	
aged ≥12 to <18 years	
Reporting group title	Cohort 2 aged ≥6 to <12 years
Reporting group description:	
aged ≥6 to <12 years	
Reporting group title	Cohort 3 aged ≥2 to <6 years
Reporting group description:	
aged ≥2 to <6 years	
Reporting group title	Cohort 4 aged ≥3 months to <2 years
Reporting group description:	
aged ≥3 months to <2 years	

Primary: Pharmacokinetic parameters of avibactam and ceftazidime for cohort 1 and 2: AUC

ZI AUC	
End point title	Pharmacokinetic parameters of avibactam and ceftazidime for cohort 1 and 2: $AUC^{[1][2]}$
End point description:	
End point type	Primary
End point timeframe:	
Day 1	

Notes:

- [1] No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
- Justification: The data was only summarised for cohort 1 and cohort 2.
- [2] The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was only summarised for cohort 1 and cohort 2.

End point values	Cohort 1 aged ≥12 to <18 years	Cohort 2 aged ≥6 to <12 years	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	8[3]	8 ^[4]	
Units: h*ng/mL			
geometric mean (geometric coefficient of variation)			
AUC(0-8): Avibactam	35140 (± 33.11)	33590 (± 22.15)	
AUC(0-8): Ceftazidime	219100 (± 29.69)	212400 (± 16.28)	
AUC(0-t): Avibactam	36250 (± 33.7)	34380 (± 23.37)	
AUC(0-t): Ceftazidime	229200 (± 30.86)	217800 (± 18.36)	
AUC(0-inf): Avibactam	36430 (± 33.61)	34820 (± 22.62)	

AUC(0-inf): Ceftazidime	230600 (±	221200 (±	
	30.7)	17.38)	

Notes:

- [3] Pharmacokinetic analysis set. Cohorts 3 and 4 PK parameters not derived due to sparse sampling.
- [4] Pharmacokinetic analysis set. Cohorts 3 and 4 PK parameters not derived due to sparse sampling.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameters of avibactam and ceftazidime for cohort 1 and 2: Cmax

•	Pharmacokinetic parameters of avibactam and ceftazidime for cohort 1 and 2: Cmax ^{[5][6]}
End point description:	

End point type	Primary
End point timeframe:	

Day 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The data was only summarised for cohort 1 and cohort 2.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was only summarised for cohort 1 and cohort 2.

End point values	Cohort 1 aged ≥12 to <18 years	Cohort 2 aged ≥6 to <12 years	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	8 ^[7]	8[8]	
Units: ng/mL			
geometric mean (geometric coefficient of variation)			
Cmax: Avibactam	15090 (± 52.42)	14140 (± 22.96)	
Cmax: Ceftazidime	79750 (± 41.81)	81270 (± 17.81)	

Notes:

[7] - Pharmacokinetic analysis set

[8] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse e	vents:
From start of study dose infusion of	of CAZ AVI through the follow up period (Day 2 and Day 3)
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
aged ≥12 to <18 years	
Reporting group title	Cohort 2
Reporting group description:	
aged ≥6 to <12 years	
Reporting group title	Cohort 3
Reporting group description:	
aged ≥2 to <6 years	
Reporting group title	Cohort 4
Reporting group description:	
aged ≥3 months to <2 years	

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 4	
Total subjects affected by serious adverse events		
subjects affected / exposed	0 / 8 (0.00%)	
number of deaths (all causes)	0	
number of deaths resulting from adverse events	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	4 / 8 (50.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural			
complications Procedural site reaction			
subjects affected / exposed	0 / 0 / 0 000/)	0 / 0 /0 000/)	0 / 0 / 0 000/)
	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 4	

Total subjects affected by non-serious adverse events		
subjects affected / exposed	2 / 8 (25.00%)	
Investigations		
Alanine aminotransferase increased		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	
Aspartate aminotransferase increased		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	
Blood triglycerides increased		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	
Gamma-glutamyltransferase increased		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	
Injury, poisoning and procedural complications		
Procedural site reaction		
subjects affected / exposed	1 / 8 (12.50%)	
occurrences (all)	1	
	_	
Cardiac disorders		
Sinus tachycardia		
subjects affected / exposed	1 / 8 (12.50%)	
occurrences (all)	1	
	_	
Gastrointestinal disorders		
Constipation		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	
Diarrhoea		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)		
occurrences (aii)	0	
Vomiting		
subjects affected / exposed	0 / 8 (0.00%)	
occurrences (all)	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2013	Amended to clarify the timing of protocol assessments (to provide clarification on the timing of protocol assessments and the allowable window of time around vital sign measurements). Amended inclusion criterion #3 with respect to early hospital discharge (to address realistic timelines for patient discharge and clarify that hospitalization was only mandatory for the first 24 hours after infusion. An early discharge was possible if the patient was able to return to the hospital or clinic for assessments on Day 3). Amended exclusion criterion #10 with respect to the upper limit BMI. Amended accountability language (Section 5.7.1 of the CSP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported