



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)	-

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)	EMA-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:

Subjects enrolled per age group

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.

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:

2000 mg 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.

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 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.

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 ≥ 40 kg) or 12.5 mg/kg (patients < 40 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:

2000 mg (patients ≥ 40 kg) or 50 mg/kg (patients < 40 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 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:

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 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

patients with moderate renal insufficiency the dose for both ceftazidime and avibactam was halved

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	-

Baseline characteristics

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	

Reporting group values	Cohort 1 aged ≥ 12 to < 18 years	Cohort 2 aged ≥ 6 to < 12 years	Cohort 3 aged ≥ 2 to < 6 years
Number of subjects	8	8	8
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	8	8
Adolescents (12-17 years)	8	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	14.945	8.02	3.519
standard deviation	± 1.5599	± 1.4036	± 1.0044
Gender, Male/Female			
Units: participants			
Female	5	3	6
Male	3	5	2
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	0
White	6	6	7
More than one race	0	0	0
Unknown or Not Reported	0	0	0

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

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

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 (\pm 33.11)	33590 (\pm 22.15)		
AUC(0-8): Ceftazidime	219100 (\pm 29.69)	212400 (\pm 16.28)		
AUC(0-t): Avibactam	36250 (\pm 33.7)	34380 (\pm 23.37)		
AUC(0-t): Ceftazidime	229200 (\pm 30.86)	217800 (\pm 18.36)		
AUC(0-inf): Avibactam	36430 (\pm 33.61)	34820 (\pm 22.62)		

AUC(0-inf): Ceftazidime	230600 (\pm 30.7)	221200 (\pm 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

End point title	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 (\pm 52.42)	14140 (\pm 22.96)		
Cmax: Ceftazidime	79750 (\pm 41.81)	81270 (\pm 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 events:

From start of study dose infusion 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 occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Injury, poisoning and procedural complications			
Procedural site reaction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Cardiac disorders			
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 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 occurrences (all)	0 / 8 (0.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injury, poisoning and procedural complications			
Procedural site reaction subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Cardiac disorders			
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 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