Clinical trial results:
A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections

Summary

EudraCT number	2011-003812-22
Trial protocol	Outside EU/EEA LT LV ES PL
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	P903-23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01400867
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cerexa, Inc (a subsidiary of Allergan, plc)
Sponsor organisation address	185 Hudson Street, Plaza 5, Jersey City, United States, NJ 07302-3908
Public contact	Clinical Trial Registry Team, Cerexa, Inc (a subsidiary of Allergan, plc), +1 877-277-8566, khaeckl@cerexa.com
Scientific contact	Clinical Trial Registry Team, Cerexa, Inc (a subsidiary of Allergan, plc), +1 877-277-8566, khaeckl@cerexa.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000769-PIP01-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2014
Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of ceftaroline versus comparator in pediatric subjects ages 2 months to < 18 years with acute bacterial skin and skin structure infections (ABSSSI)

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. Written informed consent from parent or legally acceptable representative and verbal informed assent from subject (if age appropriate and according to local requirements) were obtained before initiating study-related assessments or procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2011
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	Poland: 19
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Latvia: 21
Country: Number of subjects enrolled	Lithuania: 12
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Georgia: 31
Worldwide total number of subjects	163
EEA total number of subjects	64

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	39
Children (2-11 years)	87
Adolescents (12-17 years)	37
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 163 subjects between the ages of 2 months to < 18 years, with acute bacterial skin and skin structure infections (ABSSSI) were enrolled in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Investigator, Assessor[2]

Blinding implementation details:

At each study centre, at least 1 blinded investigator ("Blinded Observer") did not know the subject's treatment assignment and conducted clinical assessments (including efficacy and safety).

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftaroline fosamil

Arm description:

110 subjects were randomized (ITT) to receive a minimum of 7 IV doses of ceftaroline fosamil (a minimum of 3 days of IV therapy). A switch to open-label oral study drug (cephalexin [preferred oral switch], clindamycin, or linezolid) was allowed on or after Study Day 4 if a subject met the protocol-specified criteria. The total duration of IV plus PO therapy was 5 to 14 days.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV ceftaroline fosamil was infused over 60 (± 10) minutes every 8 hours (q8h) (± 1 hour) as follows:
Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
Children < 6 months: ceftaroline fosamil 8 mg/kg

Arm title	Comparator

Arm description:

53 subjects were randomized (ITT) to receive vancomycin or cefazolin with or without aztreonam for a minimum of 3 days of IV therapy. A switch to open-label oral study drug (cephalexin [preferred oral switch], clindamycin, or linezolid) was allowed on or after Study Day 4 if a subject met the protocol specified criteria. The total duration of IV plus PO therapy was 5 to 14 days.

Arm type	Active comparator
Investigational medicinal product name	Vancomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV vancomycin 15 mg/kg every 6 hours (q6h) (± 1 hour) was infused over at least 60 minutes (or at a maximum of 10 mg/min, whichever was longer).

Investigational medicinal product name	Cefazolin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV cefazolin 75 mg/kg/day divided q8h (± 1 hour) was infused over 60 (± 10) minutes.

Investigational medicinal product name	Aztreonam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV aztreonam 30 mg/kg q8h (± 1 hour) was infused over 60 (± 10) minutes, at any time during IV therapy if an infection involving a Gram-negative pathogen was identified or suspected.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This study was observer-blinded. At each study centre, at least 1 blinded investigator did not know the subject's treatment assignment and conducted clinical assessments (including efficacy and safety).
[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This study was observer-blinded. At each study centre, at least 1 blinded investigator did not know the subject's treatment assignment and conducted clinical assessments (including efficacy and safety).

Number of subjects in period 1	Ceftaroline fosamil	Comparator
Started	110	53
Completed	103	48
Not completed	7	5
Consent withdrawn by subject	5	2
Other reason	2	-
Lost to follow-up	-	2
Subject didn't meet inclusion/exclusion criteria	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	163	163	
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)	39	39	
Children (2-11 years)	87	87	
Adolescents (12-17 years)	37	37	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	73	73	
Male	90	90	

Subject analysis sets	
Subject analysis set title	Ceftaroline - Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all patients received any amount of IV study drug.

Subject analysis set title	Comparator - Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all patients received any amount of IV study drug.

Subject analysis set title	Ceftaroline - MITT Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) Population consists of all patients who received any amount of study drug and have confirmed diagnosis of ABSSSI.

Subject analysis set title	Comparator - MITT Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) Population consists of all patients who received any amount of study drug and have confirmed diagnosis of ABSSSI.

Subject analysis set title	Ceftaroline - Clinically Evaluable Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Clinically Evaluable (CE) population consists of all patients in the ITT population who also meet minimal ABSSSI disease criteria and all evaluability criteria.

Subject analysis set title	Comparator - Clinically Evaluable Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Clinically Evaluable (CE) population consists of all patients in the ITT population who also meet the minimal ABSSSI disease criteria and all evaluability criteria.

Reporting group values	Ceftaroline - Safety Set	Comparator - Safety Set	Ceftaroline - MITT Set
Number of subjects	106	53	107
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)	24	13	25
Children (2-11 years)	59	27	59
Adolescents (12-17 years)	23	13	23
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	50	21	50
Male	56	32	57

Reporting group values	Comparator - MITT Set	Ceftaroline - Clinically Evaluable Set	Comparator - Clinically Evaluable Set
Number of subjects	52	96	45
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)	12	19	10
Children (2-11 years)	27	57	26
Adolescents (12-17 years)	13	20	9
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	21	45	18
Male	31	51	27

End points

End points reporting groups

Reporting group title	Ceftaroline fosamil

Reporting group description:

110 subjects were randomized (ITT) to receive a minimum of 7 IV doses of ceftaroline fosamil (a minimum of 3 days of IV therapy). A switch to open-label oral study drug (cephalexin [preferred oral switch], clindamycin, or linezolid) was allowed on or after Study Day 4 if a subject met the protocol-specified criteria. The total duration of IV plus PO therapy was 5 to 14 days.

Reporting group title	Comparator

Reporting group description:

53 subjects were randomized (ITT) to receive vancomycin or cefazolin with or without aztreonam for a minimum of 3 days of IV therapy. A switch to open-label oral study drug (cephalexin [preferred oral switch], clindamycin, or linezolid) was allowed on or after Study Day 4 if a subject met the protocol specified criteria. The total duration of IV plus PO therapy was 5 to 14 days.

Subject analysis set title	Ceftaroline - Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all patients received any amount of IV study drug.

Subject analysis set title	Comparator - Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all patients received any amount of IV study drug.

Subject analysis set title	Ceftaroline - MITT Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) Population consists of all patients who received any amount of study drug and have confirmed diagnosis of ABSSSI.

Subject analysis set title	Comparator - MITT Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) Population consists of all patients who received any amount of study drug and have confirmed diagnosis of ABSSSI.

Subject analysis set title	Ceftaroline - Clinically Evaluable Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Clinically Evaluable (CE) population consists of all patients in the ITT population who also meet minimal ABSSSI disease criteria and all evaluability criteria.

Subject analysis set title	Comparator - Clinically Evaluable Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Clinically Evaluable (CE) population consists of all patients in the ITT population who also meet the minimal ABSSSI disease criteria and all evaluability criteria.

Primary: Extent of Exposure - Safety Set

End point title	Extent of Exposure - Safety Set[1]

End point description:

Extent of Exposure is described as number of Calendar Days subjects received ceftaroline or comparator (IV or Oral).

End point type	Primary

End point timeframe:

The Extent of Exposure was evaluated from the date of the first dose of specified study drug to the date of the last dose of specified study drug + 1 day.

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: This was an exploratory study with an emphasis on safety and was not powered for comparative inferential analysis.

End point values	Ceftaroline - Safety Set	Comparator - Safety Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	53		
Units: Number of patients				
< 3 days	2	2		
3 - 5 days	11	8		
6 - 8 days	26	15		
9 - 15 days	63	28		
> 15 days	4	0		

Statistical analyses

No statistical analyses for this end point

Primary: Adverse Events - Safety Set

End point title	Adverse Events - Safety Set[2]

End point description:

The safety assessment includes monitoring of adverse events, serious adverse events, deaths, and discontinuations due to AEs, including cephalosporin class effects and additional AEs.

End point type	Primary

End point timeframe:

Adverse Events (AEs) were evaluated from signing of the ICF through LFU visit (21 to 35 days after last dose of any study drug [IV or PO]). Cephalosporin class effects and additional AEs were closely monitored/followed until resolution or stabilization.

Notes:

[2] - 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: This is an exploratory study with an emphasis on safety and is not powered for inferential statistical
analysis.

End point values	Ceftaroline - Safety Set	Comparator - Safety Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	53		
Units: Number of patients				
Subjects with any TEAE	51	23		
Subjects with any drug-related TEAEs	23	12		
Subjects with any SAEs	4	1		
Subjects with any drug-related SAEs	2	0		
Discontinuations of any study drug due to AE	4	2		

Discontinuation of any IV study drug due to AE	2	1		
Deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response at Study Day 3 - MITT Set

End point title	Clinical Response at Study Day 3 - MITT Set

End point description:

Clinical Response at Day 3 is defined as ≥ 20% reduction from baseline in infection area (length × width).

End point type	Secondary

End point timeframe:

Clinical Response at Study Day 3 was evaluated from Study Day 1 (the first day of IV study drug administration) to Study Day 3.

End point values	Ceftaroline - MITT Set	Comparator - MITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: Number of patients				
Responder	91	44		
Non-responder	11	4		
Incomplete data	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response at Study Day 3 - MITT Set

End point title	Clinical Response at Study Day 3 - MITT Set

End point description:

Clinical response at Study Day 3 was measured by cessation of spread relative to baseline as measured by area.

End point type	Secondary

End point timeframe:

Clinical Response at Study Day 3 was evaluated from Study Day 1 (the first day of IV study drug administration) to Study Day 3.

End point values	Ceftaroline - MITT Set	Comparator - MITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: Number of patients				
Responder	98	47		
Non-responder	4	1		
Incomplete data	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response at Study Day 3 - MITT Set

End point title	Clinical Response at Study Day 3 - MITT Set

End point description:

Clinical Response was measured by cessation of spread relative to baseline as measured by length and width, separately, AND temperature < 37.6°C, on Study Day 3, irrespective of temperature collection method.

End point type	Secondary

End point timeframe:

Clinical Response at Study Day 3 was evaluated from Study Day 1 (the first day of IV study drug administration) to Study Day 3.

End point values	Ceftaroline - MITT Set	Comparator - MITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: Number of patients				
Responder	86	39		
Non-responder	16	9		
Incomplete data	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcome at TOC - MITT Set

End point title	Clinical Outcome at TOC - MITT Set

End point description:

Clinical Outcome at TOC is defined as assessment of clinical cure, clinical failure and indeterminate for the MITT population at Test-Of-Cure.

End point type	Secondary

End point timeframe:

Clinical Outcome at Test-of-Cure (TOC) was evaluated 8 to 15 days after administration of the last dose of any study drug [IV or PO].

End point values	Ceftaroline - MITT Set	Comparator - MITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: Number of patients				
Clinical cure	101	45		
Clinical failure	0	1		
Indeterminate	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcomes at TOC - Clinically Evaluable Set

End point title	Clinical Outcomes at TOC - Clinically Evaluable Set

End point description:

Clinical Outcome at TOC is defined as assessment of clinical cure, clinical failure and indeterminate for the Clinically Evaluable population at Test-of-Cure.

End point type	Secondary

End point timeframe:

Clinical Outcomes at Test-of-Cure (TOC) were evaluated 8 to 15 days after the last dose of any study drug [IV or PO].

End point values	Ceftaroline - Clinically Evaluable Set	Comparator - Clinically Evaluable Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	45		
Units: Number of patients				
Clinical cure	96	44		
Clinical failure	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

21 to 35 days after last dose of any study drug [IV or PO]). If the LFU was conducted < 30 days after the last dose of study drug or was not conducted, AE/SAE information is obtained by telephone 30 days after the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Ceftaroline - Safety Population
Reporting group description: -	
Reporting group title	Comparator - Safety Population

Reporting group description: -

Serious adverse events	Ceftaroline - Safety Population	Comparator - Safety Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 106 (3.77%)	1 / 53 (1.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 106 (0.94%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 106 (0.94%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 106 (0.94%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ceftaroline - Safety Population	Comparator - Safety Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 106 (21.70%)	19 / 53 (35.85%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 106 (7.55%)	8 / 53 (15.09%)	
occurrences (all)	8	8	
Vomiting			
subjects affected / exposed	7 / 106 (6.60%)	8 / 53 (15.09%)	
occurrences (all)	7	8	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 106 (7.55%)	2 / 53 (3.77%)	
occurrences (all)	8	2	
Pruritus			
subjects affected / exposed	1 / 106 (0.94%)	3 / 53 (5.66%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2011	The following changes were implemented with Amendment 1: removal of the requirement for ABSSSI specimens to be collected on all subjects; revision of the dosing regimen for study drug and PK sampling schedule. In addition, minor changes were made for clarity, consistency, and/or accuracy.
17 April 2012	The following changes were implemented with Amendment 2: addition of linezolid as a second option for PO study drug therapy; addition of the option for subjects who start the study on intravenous (IV) vancomycin and for whom no MRSA is identified to switch to IV cefazolin; addition of a clinical laboratory assessment time point and test to further evaluate safety; updates dosing regimen for cohorts and other clarifications. In addition, minor changes were made for clarity, consistency, and/or accuracy.
20 September 2012	The following changes were implemented with Amendment 3: addition of dosing information for Cohort 4; removal of the requirement for 3 days of hospitalization for enrolment; change in outpatient parenteral antimicrobial therapy (OPAT) criteria for clarification and modification of the lesion area and margin calculations requirements. In addition, minor changes were made for clarity, consistency, and/or accuracy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported