Clinical trial results:
Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis

Summary

EudraCT number	2014-003243-34
Trial protocol	HU ES IT LT
Global end of trial date	30 December 2017

Results information

Result version number	v1
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	C2661002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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?	Yes
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	23 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, pharmacokinetics, and efficacy of Ceftaroline in neonates and young infants with late-onset sepsis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 August 2015
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: 4
Country: Number of subjects enrolled	Hungary: 7
Worldwide total number of subjects	11
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	7
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	0
Adolescents (12-17 years)	0
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:

The study was conducted in the United States and Hungary from 04 August 2015 to 26 December 2017. A total of 11 subjects were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftaroline Fosamil: Young Infants

Arm description:

Young infants aged greater than (>) 28 days to less than (<) 60 days, received ceftaroline fosamil infusion, intravenously (IV) at a dose of 4 milligrams per kilogram (mg/kg) or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Arm type	Experimental
Investigational medicinal product name	Ampicillin
Investigational medicinal product code	
Other name	ampicillin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ampicillin IV is mandatory for 48 hours if the presence of an organism that requires treatment with ampicillin cannot be excluded. Given per standard of care.

Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Ceftaroline fosamil 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours for 48 hours to 14 days plus ampicillin IV for 48 hours minimum and optional aminoglycoside per local standard of care therapy.

Investigational medicinal product name	Aminoglycoside
Investigational medicinal product code	
Other name	aminoglycoside
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aminoglycoside, given as standard of care therapy, is optional during the study as the discretion of the Investigator.

Arm title	Ceftaroline Fosamil: Term Neonates

Arm description:

Term Neonates (defined as gestational age greater than or equal to [>=] 37 weeks) aged 7 to less than equal to (<=28) days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Ceftaroline fosamil 6 mg/kg over 60 minutes every 8 hours for 48 hours to 14 days plus ampicillin IV for 48 hours minimum and optional aminoglycoside per local standard of care therapy.

Investigational medicinal product name	Aminoglycoside
Investigational medicinal product code	
Other name	aminoglycoside
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aminoglycoside, given as standard of care therapy, is optional during the study as the discretion of the Investigator.

Investigational medicinal product name	Ampicillin
Investigational medicinal product code	
Other name	ampicillin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ampicillin IV is mandatory for 48 hours if the presence of an organism that requires treatment with ampicillin cannot be excluded. Given per standard of care.

Arm title	Ceftaroline Fosamil: Preterm Neonates

Arm description:

Preterm neonates (defined as gestational age >=34 weeks to <37 weeks) aged 7 to <=28 days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in
combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Ceftaroline fosamil 6 mg/kg over 60 minutes every 8 hours for 48 hours to 14 days plus ampicillin IV for 48 hours minimum and optional aminoglycoside per local standard of care therapy.

Investigational medicinal product name	Ampicillin
Investigational medicinal product code	
Other name	ampicillin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ampicillin IV is mandatory for 48 hours if the presence of an organism that requires treatment with ampicillin cannot be excluded. Given per standard of care.

Investigational medicinal product name	Aminoglycoside
Investigational medicinal product code	
Other name	aminoglycoside
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aminoglycoside, given as standard of care therapy, is optional during the study as the discretion of the Investigator.

Number of subjects in period 1	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Term Neonates	Ceftaroline Fosamil: Preterm Neonates
Started	4	5	2
Completed	2	3	2
Not completed	2	2	0
Treatment stopped to be discharged home	2	2	-

Baseline characteristics

Reporting groups

Reporting group title	Ceftaroline Fosamil: Young Infants

Reporting group description:

Young infants aged greater than (>) 28 days to less than (<) 60 days, received ceftaroline fosamil infusion, intravenously (IV) at a dose of 4 milligrams per kilogram (mg/kg) or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Term Neonates

Reporting group description:

Term Neonates (defined as gestational age greater than or equal to [>=] 37 weeks) aged 7 to less than equal to (<=28) days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Preterm Neonates

Reporting group description:

Preterm neonates (defined as gestational age >=34 weeks to <37 weeks) aged 7 to <=28 days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in
combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group values	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Term Neonates	Ceftaroline Fosamil: Preterm Neonates
Number of subjects	4	5	2
Age categorical Units: Subjects			
Young infants aged >28 days to <60 days	4	0	0
Term neonates aged 7 to <=28 days	0	5	0
Pre-term neonate aged 7 to <=28 days	0	0	2
Age Continuous Units: days			
arithmetic mean	48.0	22.0	15.5
standard deviation	± 4.69	± 3.81	± 4.95
Sex: Female, Male Units: Subjects			
Female	3	1	1
Male	1	4	1
Race (NIH/OMB) Units: Subjects			
Asian	1	0	0
White	3	5	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	4	4	2

Reporting group values	Total		
Number of subjects	11		
Age categorical Units: Subjects			
Young infants aged >28 days to <60 days	4		
Term neonates aged 7 to <=28 days	5		
Pre-term neonate aged 7 to <=28 days	2		
Age Continuous Units: days			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	5		
Male	6		
Race (NIH/OMB) Units: Subjects			
Asian	1		
White	10		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	10		

End points

End points reporting groups

Reporting group title	Ceftaroline Fosamil: Young Infants

Reporting group description:

Young infants aged greater than (>) 28 days to less than (<) 60 days, received ceftaroline fosamil infusion, intravenously (IV) at a dose of 4 milligrams per kilogram (mg/kg) or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Term Neonates

Reporting group description:

Term Neonates (defined as gestational age greater than or equal to [>=] 37 weeks) aged 7 to less than equal to (<=28) days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Preterm Neonates

Reporting group description:

Preterm neonates (defined as gestational age >=34 weeks to <37 weeks) aged 7 to <=28 days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in
combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Subject analysis set title	Ceftaroline Fosamil: All Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside as per local standard of care, which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)[1]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following endpoints or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to study follow-up (SFU) visit (28 to 35 days after last dose of study treatment) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. Safety analysis set consisted of all enrolled subjects for whom informed consent form was signed and received any amount of ceftaroline fosamil.

End point type	Primary

End point timeframe:

Baseline up to SFU visit (up to a maximum study duration of 49 days)

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Term Neonates	Ceftaroline Fosamil: Preterm Neonates	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	2	
Units: subjects				
AEs	1	3	1	
SAEs	0	0	1	
Discontinuations Due to AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response

End point title	Percentage of Subjects With Favorable Clinical Response

End point description:

Clinical response was assessed by the investigator as Cure, Failure or Indeterminate at End of treatment (EOT) and Test of Cure (TOC). Favorable clinical response was defined as clinical response of Cure, defined as resolution of all acute signs and symptoms of Late-onset sepsis (LOS) or improvement to such an extent that no further antibacterial therapy is required. Eradication defined as absence of the original baseline pathogen from the source specimen; presumed eradication was defined when source specimen was not available to culture and the subject was assessed as a clinical cure (resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy was required) EOT visit occurred within 24 hours after the end of last infusion. Modified ITT analysis set: subjects who received ceftaroline fosamil and met minimal disease criteria of late-onset sepsis.

End point type	Secondary

End point timeframe:

EOT visit (within 24 hours after the end of infusion), TOC visit (8 to 15 days after last dose of study drug)

End point values	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Term Neonates	Ceftaroline Fosamil: Preterm Neonates	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	3	1	
Units: percentage of subjects				
number (confidence interval 95%)				
At EOT visit	50.0 (12.3 to 87.7)	33.3 (3.9 to 82.3)	100 (14.7 to 100)	
At TOC visit	50.0 (12.3 to 87.7)	33.3 (3.9 to 82.3)	100 (14.7 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Microbiological Response

End point title	Percentage of Subjects With Favorable Microbiological Response

End point description:

Microbiological response was determining programmatically and assessed at the subject level at EOT and TOC. Microbiological response was defined as Favorable (Eradication or Presumed Eradication), Unfavorable (Persistence or Presumed Persistence) or Indeterminate (subject's clinical response is Indeterminate and no microbiological culture data is available). Eradication defined as absence of the original baseline pathogen from the source specimen; presumed eradication was defined when source specimen was not available to culture and the subject was assessed as a clinical cure (resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy was required) EOT visit occurred within 24 hours after the end of last infusion. TOC visit occurred within 8 to 15 days after last dose of study drug. Analyzed in the mITT set.

End point type	Secondary

End point timeframe:

EOT visit (within 24 hours after the end of infusion), TOC visit (8 to 15 days after last dose of study drug)

End point values	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Term Neonates	Ceftaroline Fosamil: Preterm Neonates	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	3	1	
Units: percentage of subjects				
number (confidence interval 95%)				
At EOT visit	50.0 (12.3 to 87.7)	66.7 (17.7 to 96.1)	100 (14.7 to 100)	
At TOC visit	25.0 (2.8 to 71.6)	33.3 (3.9 to 82.3)	100 (14.7 to 100)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to SFU visit (up to a maximum study duration of 49 days)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ceftaroline Fosamil: Young Infants

Reporting group description:

Young infants aged > 28 days to <60 days, received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Preterm Neonates

Reporting group description:

Preterm neonates (defined as gestational age >=34 weeks to <37 weeks) aged 7 to <=28 days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Reporting group title	Ceftaroline Fosamil: Term Neonates

Reporting group description:

Term neonates (defined as gestational age >= 37 weeks) aged 7 to <=28 days received ceftaroline fosamil infusion, IV at a dose of 4 mg/kg or 6 mg/kg over 60 minutes every 8 hours in combination with ampicillin IV as per local standard of care, for a minimum of 48 hours and up to a maximum duration of 14 days. Along with this, subjects received an aminoglycoside which was optional and could be started and stopped at any time during the study at the discretion of investigator.

Serious adverse events	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Preterm Neonates	Ceftaroline Fosamil: Term Neonates
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			

Salmonellosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ceftaroline Fosamil: Young Infants	Ceftaroline Fosamil: Preterm Neonates	Ceftaroline Fosamil: Term Neonates
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 2 (50.00%)	3 / 5 (60.00%)
Nervous system disorders			
Cerebral cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pyelocaliectasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Otitis externa subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 2 (50.00%) 1	0 / 5 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2015	The dose of ceftaroline fosamil to be given was increased to 6 mg/kg.
25 August 2016	Inclusion criterion was revised so that subjects must only meet at least 1 of the listed laboratory criteria, rather than 2.
25 May 2017	Safety follow-up visit window changed to 28 - 35 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 December 2017	Based on the decision of PDCO and FDA, the study was terminated prematurely.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data for endpoints of plasma concentration will be estimated and reported separately as part of the population PK analysis and will be provided once available.

Notes: