Clinical trial results:
A Single Arm, Open-label Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of Cefiderocol in Hospitalized Paediatric Subjects 3 Months to < 18 Years of Age with Suspected or Confirmed Aerobic Gram-negative Bacterial Infections

Summary

EudraCT number	2019-002120-32
Trial protocol	HU BE LV
Global end of trial date	06 February 2023

Results information

Result version number	v1 (current)
This version publication date	02 December 2023
First version publication date	02 December 2023

Trial information

Trial identification

Sponsor protocol code	1802R2135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04335539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shionogi B.V.
Sponsor organisation address	Kingsfordweg 151, Amsterdam, Netherlands, 1043 GR
Public contact	Corporate Communications Department, Shionogi & Co., Ltd, +81 662097885, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Corporate Communications Department, Shionogi & Co., Ltd, +81 662097885, shionogiclintrials-admin@shionogi.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002133-PIP01-17
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	25 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized paediatric subjects 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections
- To assess the pharmacokinetics (PK) of cefiderocol after single-dose administration of cefiderocol in hospitalized paediatric subjects 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections
- To assess the safety and tolerability of cefiderocol after multiple-dose administration in hospitalized paediatric subjects 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections
- To assess the PK of cefiderocol after multiple-dose administration in hospitalized paediatric subjects 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

Protection of trial subjects:

Reviewing interim aggregate study data, individual case narratives and assessing the benefit/risk through examination of the safety of study treatments.
Advising the Company on whether the current internal assessment and approach is scientifically sound or any change should be considered (especially in the
interest of patient safety).

Background therapy:

Various standard of care therapies are permitted

Evidence for comparator:

N/A

Actual start date of recruitment	18 August 2020
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	Spain: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Georgia: 20
Worldwide total number of subjects	53
EEA total number of subjects	11

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)	12
Children (2-11 years)	34
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The single-dose phase in all 4 cohorts confirmed cefiderocol exposures in at least 6 subjects prior to conducting a multiple-dose phase (Cohorts 2, 3, and 4) in additional subjects.
Enrollment was stopped for the applicable cohort to allow for analysis of the PK data prior to moving from single-dose to multiple-dose in Cohorts 2, 3, and 4.

Pre-assignment

Screening details:

Screening occurred within 4 days prior to Treatment Day 1 or on Treatment Day 1 in both the single- and multiple-dose phase. Prior to Screening, sites were asked to send a Permission to Screen Form containing limited information of the potential subject to Shionogi medical monitors for evaluation and agreement.

Period 1

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

Blinding implementation details:

Open label study

Arms

Arm title	study

Arm description:

All patients entered the study in a single arm

Arm type	Experimental
Investigational medicinal product name	Cefiderocol
Investigational medicinal product code	S-649266
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of cefiderocol for the Single-dose Phase was determined based on body weight only; the maximum dose to be administered was not to exceed 2000 mg.
Cefiderocol was administered as an intravenous (IV) infusion over 3 hours (in addition to SOC) at any time during the SOC treatment regimen.
The dose for the Multiple-dose Phase was determined based on both body weight and renal function; the maximum dose to be administered did not exceed 2000 mg. In the Multiple-dose Phase, cefiderocol was administered on Day 1 (in addition to SOC), within 72 hours of the start of potentially effective treatment with SOC antibiotics for infection. Participants subsequently received cefiderocol every 8 hours (q8h) as an IV infusion over 3 hours for an expected 5 to 14 days.

Number of subjects in period 1	study
Started	53
Completed	52
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)

Reporting group description: -

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	53	53	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	12	12	
Children (2-11 years)	34	34	
Adolescents (12-17 years)	7	7	
Gender categorical Units: Subjects			
Female	34	34	
Male	19	19	

End points

End points reporting groups

Reporting group title	study
Reporting group description:	
All patients entered the study in a single arm	

Primary: To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gramnegative bacterial infections

End point title	To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gramnegative bacterial infections[1]
End point description:	

End point type	Primary
End point timeframe:	
From screening to end of study	

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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: numbers	24			

Statistical analyses

No statistical analyses for this end point

Primary: To assess the safety and tolerability of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gramnegative bacterial infections

End point title	To assess the safety and tolerability of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gramnegative bacterial infections[2]
End point description:	

End point type	Primary
End point timeframe:	
From screening to end of study	

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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: numbers	29			

Statistical analyses

No statistical analyses for this end point

Primary: To assess the PK of cefiderocol after single dose administration of cefiderocol in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

End point title	To assess the PK of cefiderocol after single dose administration of cefiderocol in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections[3]

End point description:

The geometric mean concentrations and geometric SD at 3 hours after the start of infusion for the single-dose cohort across the 4 cohorts

End point type	Primary

End point timeframe:

From screening to end of study

Notes:

[3] - 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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: microgram(s)/millilitre				
geometric mean (standard deviation)	87.6 (± 1.33)			

Statistical analyses

No statistical analyses for this end point

Primary: To assess the PK of cefiderocol after single dose administration of cefiderocol in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

End point title	To assess the PK of cefiderocol after single dose administration of cefiderocol in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections[4]

End point description:

The geometric mean concentrations and geometric SD at 8 hours after the start of infusion for the single-dose cohort across the 4 cohorts

End point type	Primary

End point timeframe:

From screening to end of study

Notes:

[4] - 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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: microgram(s)/millilitre				
geometric mean (standard deviation)	9.59 (± 1.72)			

Statistical analyses

No statistical analyses for this end point

Primary: To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

End point title	To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections[5]

End point description:

The geometric mean concentrations and geometric SD at 3 hours of Day3 & Day 4 after the start of infusion for the multiple-dose cohort across the 4 cohorts

End point type	Primary

End point timeframe:

From screening to end of study

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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: microgram(s)/millilitre				
geometric mean (standard deviation)	96.2 (± 1.48)			

Statistical analyses

No statistical analyses for this end point

Primary: To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

End point title	To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections[6]

End point description:

The geometric mean concentrations and geometric SD at 8 hours of Day 3 & Day 4 after the start of infusion (before the next infusion in the multiple-dose phase) for the multiple-dose cohort across the 4 cohorts

End point type	Primary

End point timeframe:

From screening to end of study

Notes:

[6] - 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: There was no comparison in this study

End point values	study			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: microgram(s)/millilitre				
geometric mean (standard deviation)	13.8 (± 2.31)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From screening to end of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	All subjects
Reporting group description: All subjects enrolled and receiving administration of study drug	

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 52 (1.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 52 (23.08%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Congenital, familial and genetic disorders Laryngomalacia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Haematochezia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		

Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	 2 / 52 (3.85%) 2		
Infections and infestations Candida infection subjects affected / exposed occurrences (all) Pneumocystis jirovecii infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Purulent discharge subjects affected / exposed occurrences (all) Respiratory syncytial virus infection subjects affected / exposed occurrences (all) Staphylococcal bacteraemia subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Product issues Device connection issue subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2019	1
11 October 2019	2
28 April 2020	3
19 January 2021	4
04 March 2021	5
18 November 2021	6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported