Clinical trial results:
A Phase I, open-label, multi-centre study to determine the Pharmacokinetics and safety of solithromycin as add-on therapy in adolescents and children with suspected or confirmed bacterial infection.

Summary

EudraCT number	2014-004041-26
Trial protocol	Outside EU/EEA
Global end of trial date	12 October 2016

Results information

Result version number	v1 (current)
This version publication date	25 January 2018
First version publication date	25 January 2018

Trial information

Trial identification

Sponsor protocol code	CE01-120

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268279
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cempra Pharmaceuticals
Sponsor organisation address	6320 Quadrangle Drive, Suite 360, Chapel Hill, United States, 27517
Public contact	clinicaltrials@melinta.com, Cempra Pharmaceuticals, Inc, clinicaltrials@melinta.com
Scientific contact	Clinical Trials Info, Cempra Pharmaceuticals, Inc, clinicaltrials@melinta.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001581-PIP01-13
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	07 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2016
Global end of trial reached?	Yes
Global end of trial date	12 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the safety and PK profile of solithromycin (IV and oral) in the paediatric population.

Protection of trial subjects:

Solithromycin was administered orally and IV based on weight as add-on to antimicrobial agents administered per routine standard of care to adolescents and children with a suspected or confirmed infection with organisms against which solithromycin was expected to be active.

Background therapy:

The most frequently used concomitant medications included dornase alfa, fluticasone, salbutamol, piperacillin, amoxicillin, ampicillin, azithromycin, cefepime, clindamycin, vancomycin, ceftriaxone, acetaminophen, sodium chloride.

Evidence for comparator:

Not applicable

Actual start date of recruitment	03 March 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	Bulgaria: 13
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	84
EEA total number of subjects	13

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)	23
Children (2-11 years)	51
Adolescents (12-17 years)	10
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled from 34 study sites: 31 in the United States and 3 in Bulgaria.

Pre-assignment

Screening details:

1. < 18 years of age
2. Suspected or confirmed bacterial infection with organisms against which solithromycin was expected to be active
3. No consumption of Seville oranges, grapefruit 7 days before the first dose of study drug
4. Serum creatinine < 2 mg/dL
5. No hepatic dysfunction (ALT or AST > 3 x upper normal limit or direct bilirubin > ULN

Period 1

Period 1 title	All subject (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral suspension formulation

Arm description: -

Arm type	Experimental
Investigational medicinal product name	solithromycin
Investigational medicinal product code	CEM-101
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

15 mg/kg/day (0 to < 12 years) for up to 5 days.
The maximum Day 1 dose could not exceed 800 mg, and Days 2-5 could not exceed 400 mg.

Arm title	IV formulation

Arm description: -

Arm type	Experimental
Investigational medicinal product name	solithromycin
Investigational medicinal product code	CEM-101
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg/day (12 to < 18 years), 7 mg/kg/day (6 to < 12 years or < 1 month), 8 mg/kg/day (2 to < 6 years or 1 month to < 2 years) for up to 5 days.

Arm title	Oral capsule formulation

Arm description: -

Arm type	Experimental

Investigational medicinal product name	solithromycin
Investigational medicinal product code	CEM-101
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

15 mg/kg/day (6 to < 12 years) for up to 5 days.
The maximum Day 1 could not exceed 800 mg, and Days 2-5 doses could not exceed 400 mg.

Number of subjects in period 1	Oral suspension formulation	IV formulation	Oral capsule formulation
Started	40	34	10
Completed	40	34	10

Baseline characteristics

Reporting groups	
Reporting group title	All subject

Reporting group description: -

Reporting group values	All subject	Total	
Number of subjects	84	84	
Age categorical Units: Subjects			
Adolescents (12-17 years)	10	10	
6 to < 12 years	34	34	
2 to < 6 years	17	17	
0 to < 2 years	23	23	
Age continuous Units: years			
arithmetic mean	5.9		
standard deviation	± 4.6	-	
Gender categorical Units: Subjects			
Female	41	41	
Male	43	43	

End points

End points reporting groups

Reporting group title	Oral suspension formulation
Reporting group description: -	
Reporting group title	IV formulation
Reporting group description: -	
Reporting group title	Oral capsule formulation
Reporting group description: -	

Primary: IV dose determination

End point title	IV dose determination[1][2]

End point description:

End point type	Primary

End point timeframe:

For the IV formulation, PK samples collected on Days 1, 3, 4 and 5.
For the IV-to-PO switch: PK samples collected on Day 1, last day of IV dosing, first day of PO dosing and last day of PO dosing.

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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the IV dose determination.
[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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the IV dose determination.

End point values	IV formulation			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: mg/kg				
patients ages 12 to < 17 years	8			
patients ages 6 to < 12 years	8			
patients ages 2 to < 6 years	8			
patients ages 0 to < 2 years	8			

Statistical analyses

No statistical analyses for this end point

Primary: Capsule loading dose determination

End point title	Capsule loading dose determination[3][4]

End point description:

End point type	Primary

End point timeframe:

PK samples collected on Days 1, 3, 4 and 5.

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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the capsule loading dose determination.
[4] - 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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the capsule dose determination.

End point values	Oral capsule formulation			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mg/kg				
patients ages 6 to < 12 years	20			

Statistical analyses

No statistical analyses for this end point

Primary: Capsule maintenance dose determination

End point title	Capsule maintenance dose determination[5][6]

End point description:

End point type	Primary

End point timeframe:

PK samples collected on Days 1, 3, 4 and 5.

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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the capsule dose determination.
[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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the capsule maintenance dose determination.

End point values	Oral capsule formulation			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mg/kg				
patients ages 6 to < 12 years	10			

Statistical analyses

No statistical analyses for this end point

Primary: Oral suspension loading dose determination

End point title	Oral suspension loading dose determination[7][8]

End point description:

End point type	Primary

End point timeframe:

PK samples collected on Days 1, 3, 4 and 5.

Notes:

[7] - 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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the oral suspension loading dose determination.
[8] - 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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the oral suspension loading dose determination from infants to adolescents (0-17 years).

End point values	Oral suspension formulation			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: mg/kg				
patients ages 6 to < 12 years	20			
patients ages 2 to < 6 years	20			
patients ages 0 to < 2 years	20			

Statistical analyses

No statistical analyses for this end point

Primary: Oral suspension maintenance dose determination

End point title	Oral suspension maintenance dose determination[9][10]

End point description:

End point type	Primary

End point timeframe:

PK samples collected on Days 1, 3, 4 and 5.

Notes:

[9] - 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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the oral suspension maintenance dose determination.

[10] - 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: Data from this trial were merged with adolescent PK data from CE01-119 study, and a population PK analysis was performed using the software NONMEM.
PK simulation were performed to guide recommendations for the oral suspension maintenance dose determination from infants to adolescents (0-17 years).

End point values	Oral suspension formulation			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: mg/kg				
patients ages 6 to < 12 years	10			
patients ages 2 to < 6 years	10			
patients ages 0 to < 2 years	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study drug administration to late follow-up visit (day 14 +/- 4).

Adverse event reporting additional description:

If for any reason the patient could not return for the last follow-up visit and have the study procedures performed, the study staff were to contact the patient/parent/legally authorized representative (LAR) by telephone or other interactive technology.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who received at least 1 dose of study drug.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 84 (3.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia	Additional description: This SAE was experienced by the same patient who had a device occlusion.		
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Cellulitis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2.3 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 84 (47.62%)		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 84 (4.76%)		
occurrences (all)	5		
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	3 / 84 (3.57%)		
occurrences (all)	3		
infusion site pain			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	3		
Infusion site phlebitis			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	2		
medical device complication			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	2		
pyrexia			

subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 84 (2.38%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 6 / 84 (7.14%) 6 3 / 84 (3.57%) 3 2 / 84 (2.38%) 2 2 / 84 (2.38%) 2 2 / 84 (2.38%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 2 / 84 (2.38%) 2		
Skin and subcutaneous tissue disorders Skin irritation subjects affected / exposed occurrences (all)	 2 / 84 (2.38%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported