Clinical trial results:
A Phase 2/3, Randomized, Open-Label, Multi-center Study to Determine the Safety and Efficacy of Solithromycin in Adolescents (12 to 17 years of age, inclusive) and Children (2 months to <12 years of age) with Suspected or Confirmed Community-Acquired Bacterial Pneumonia

Summary

EudraCT number	2014-004039-37
Trial protocol	Outside EU/EEA GB HU ES
Global end of trial date	07 April 2018

Results information

Result version number	v1 (current)
This version publication date	14 November 2018
First version publication date	14 November 2018

Trial information

Trial identification

Sponsor protocol code	CE01-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02605122
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cempra Pharmaceuticals Inc., a wholly owned subsidiary of Melinta Therapeutics, Inc.
Sponsor organisation address	6340 Quadrangle Drive, Suite 100, Chapel Hill, United States, 27517
Public contact	Regulatory Department, Chiltern International Ltd, regulatory.service@chiltern.com
Scientific contact	Regulatory Department, Chiltern International Ltd, regulatory.service@chiltern.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 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2018
Global end of trial reached?	Yes
Global end of trial date	07 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of solithromycin in adolescents and children with Community-Acquired Bacterial Pneumonia (CABP)

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child appropriate language was provided and explained to the child. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight.

Background therapy: -

Evidence for comparator:

Multiple standard of care comparators were used per protocol for the treatment of CABP.

Actual start date of recruitment	06 September 2016
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	Bulgaria: 27
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Philippines: 16
Worldwide total number of subjects	97
EEA total number of subjects	51

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)	6
Children (2-11 years)	49
Adolescents (12-17 years)	42
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period from September 2016- March 2018. The study was terminated after 97 subjects were enrolled.

Pre-assignment

Screening details:

Subjects were randomized to either Solithromycin or an active comparator.

Period 1

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

Blinding implementation details:

A health care provider designated as a sub-investigator blinded to treatment allocation at the site documented clinical response at specified time points during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Solithromycin

Arm description:

Solithromycin for 5-7 days.

Arm type	Experimental
Investigational medicinal product name	Solithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Powder for oral suspension, Powder for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Capsules, up to 800 mg dose on Day 1 and up to 400 mg daily thereafter.
IV, 8 mg/kg daily.
Oral Suspension, 20 mg/kg on Day 1 and 10 mg/kg daily thereafter.

Arm title	Comparator

Arm description:

Comparators were dosed according to age and were consistent with current recommendations for treatment of CABP in children per site standard of care.

Arm type	Active comparator
Investigational medicinal product name	Ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Per site standard of care.

Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details: Per site standard of care.	
Investigational medicinal product name	Amoxicillin-Clavulanic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension, Powder for infusion
Routes of administration	Intravenous use, Oral use
Dosage and administration details: Per site standard of care.	
Investigational medicinal product name	Ampicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details: Per site standard of care.	
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection, Powder for oral suspension
Routes of administration	Intravenous use, Oral use
Dosage and administration details: Per site standard of care.	
Investigational medicinal product name	Erythromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Powder for oral suspension
Routes of administration	Intravenous use, Oral use
Dosage and administration details: Per site standard of care.	
Investigational medicinal product name	Erythromycin lactobionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Powder for oral suspension
Routes of administration	Intravenous use, Oral use
Dosage and administration details: Per site standard of care.	

Number of subjects in period 1	Solithromycin	Comparator
Started	73	24
Completed	68	22
Not completed	5	2
Consent withdrawn by subject	4	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Subjects who meet all inclusion/exclusion criteria and sign the informed consent/assent were enrolled. Subjects were randomized to receive solithromycin or a comparator antibiotic, administered IV and/or by mouth (PO) based on weight and age. Subjects were treated daily for 5 to 7 days with oral solithromycin and 5 to 7 days with IV or IV-to-oral solithromycin. Subjects were treated for 5 to 10 days with comparator antibiotics. Subjects received safety and efficacy assessments during and after treatment.

Reporting group values	Overall Study	Total	
Number of subjects	97	97	
Age categorical Units: Subjects			
Children (2-11 years)	49	49	
Adolescents (12-17 years)	42	42	
Infants and toddlers (2 month-23 months)	6	6	
Gender categorical Units: Subjects			
Female	40	40	
Male	57	57	

End points

End points reporting groups	
Reporting group title	Solithromycin
Reporting group description:	
Solithromycin for 5-7 days.	
Reporting group title	Comparator
Reporting group description:	
Comparators were dosed according to age and were consistent with current recommendations for treatment of CABP in children per site standard of care.	

Primary: TEAEs through Day 16 and TESAEs through Day 28	
End point title	TEAEs through Day 16 and TESAEs through Day 28
End point description:	
Summary of subjects experiencing a TEAE through Day 16 visit and TESAEs through Day 28 visit (28 days ±4 days after randomization).	
End point type	Primary
End point timeframe:	
Treatment through Day 28 (28 days +/- 4 days after randomization).	

End point values	Solithromycin	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	24		
Units: Subjects				
TEAE	24	7		
TESAE	1	1		

Statistical analyses

Statistical analysis title	Summary of Subjects Experiencing a TEAE and TESAE
Comparison groups	Solithromycin v Comparator
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Clopper-Pearson
Parameter estimate	Proportion experiencing TEAE or TESAE
Point estimate	34.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	23
upper limit	47

Notes:

[1] - No statistical test was performed.

Secondary: Clinical Improvement on Day 3-4

End point title	Clinical Improvement on Day 3-4

End point description:

Early Clinical Response was defined using the latest efficacy evaluation from Day 2 (if subject discharged prior to Day 2), Day 3, or Day 4, and was defined as improvement in at least 1 presenting sign/symptom of CABP with no deterioration in any signs/symptoms of CABP and no requirement for an additional antibiotic.

End point type	Secondary

End point timeframe:

During treatment Day 3 or 4

End point values	Solithromycin	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	15		
Units: Subjects				
Subjects achieving early Clinical Response	34	7		

Statistical analyses

Statistical analysis title	Summary of Clinical Efficacy
Comparison groups	Solithromycin v Comparator
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Clopper-Pearson
Parameter estimate	Achievement of Early Clinical Response
Point estimate	62.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	49
upper limit	74

Notes:

[2] - No statistical test was performed.

Secondary: Clinical Improvement on the last day of treatment (+ 48 hours)

End point title	Clinical Improvement on the last day of treatment (+ 48 hours)

End point description:

Clinical improvement was assessed using the latest efficacy evaluation conducted on last day of treatment (+ 48 hrs), and was defined identically to early clinical response.

End point type	Secondary

End point timeframe:

Last day of treatment (+ 48 hours)

End point values	Solithromycin	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	21		
Units: Subjects				
Subjects achieving Clinical Improvement	40	17		

Statistical analyses

Statistical analysis title	Summary of Clinical Efficacy
Comparison groups	Solithromycin v Comparator
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Clopper-Pearson
Parameter estimate	Achievement of Clinical Improvement
Point estimate	68.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	58
upper limit	78

Notes:

[3] - No statistical test was performed.

Secondary: Clinical cure during short-term follow-up at 16 days (+/- 4 days)

End point title	Clinical cure during short-term follow-up at 16 days (+/- 4 days)

End point description:

Clinical cure was assessed using the latest efficacy evaluation conducted on Day 16 (± 4 days) post-randomization, and was defined as resolution of all presenting signs/symptoms of CABP (excluding cough), no development of new signs/symptoms of CABP, and no requirement for an additional antibiotic.

End point type	Secondary

End point timeframe:

Short-term follow-up at 16 days (+/- 4 days).

End point values	Solithromycin	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	19		
Units: Subjects				
Subjects achieving Clinical Cure	36	13		

Statistical analyses

Statistical analysis title	Summary of Clinical Efficacy
Comparison groups	Solithromycin v Comparator
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[4]
Method	Clopper-Pearson
Parameter estimate	Achievement of Clinical Cure
Point estimate	62
Confidence interval	
level	95 %
sides	2-sided
lower limit	50
upper limit	73

Notes:

[4] - No statistical test was performed.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: September 2016 to April 2018	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Solithromycin
Reporting group description: -	
Reporting group title	Comparator
Reporting group description: -	

Serious adverse events	Solithromycin	Comparator	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 70 (1.43%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (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	0 / 70 (0.00%)	1 / 24 (4.17%)	
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: 1 %

Non-serious adverse events	Solithromycin	Comparator	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 70 (34.29%)	7 / 24 (29.17%)	
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed	3 / 70 (4.29%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	5 / 70 (7.14%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 70 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Infusion Site Pain			
subjects affected / exposed	6 / 70 (8.57%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
Infusion Site Pruritus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infusion Site Urticaria			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injection Site Reaction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Oedema Peripheral			

subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 70 (1.43%)	4 / 24 (16.67%)	
occurrences (all)	1	4	
Abdominal Discomfort			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rhinitis Allergic			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Rash Erythematous			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rash Maculo-Papular			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Pneumonia Viral			
subjects affected / exposed	0 / 70 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Bacteraemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infectious Pleural Effusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2017	Amendment incorporates additional safety laboratory evaluations along with new and updated dosing information for all 3 formulations of solithromycin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 April 2018	Notification of stop to recruitment and plan for early termination.	-

Notes:

Limitations and caveats

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

The study was discontinued early due to a company business decision. Study discontinuation was not related to safety or tolerability.

Notes: