Clinical trial results:
A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Linezolid IV/PO for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

Summary

EudraCT number	2013-003644-23
Trial protocol	LV HU ES PL GR HR
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	09 July 2017
First version publication date	09 July 2017

Trial information

Trial identification

Sponsor protocol code	PTK0796-ABSI-1108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02378480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Paratek Pharma LLC
Sponsor organisation address	75 Park Plaza, Boston, United States, MA, 02116
Public contact	Head of Research and Development, Paratek Pharma LLC, +1 617275-0040 ,
Scientific contact	Head of Research and Development, Paratek Pharma LLC, +1 617275-0040 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	24 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2016
Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate that omadacycline 100 mg iv every 12 hours (q12h) for 2 doses, followed by 100 mg iv every 24 hours (q24h)/300 mg po q24h is non-inferior to linezolid 600 mg iv q12h/600 mg po q12h in the treatment of adults with ABSSSI known or suspected to be due to Gram-positive pathogens

Protection of trial subjects:

The switching from i.v. to p.o. treatment, the first dose of p.o. therapy should begin in the morning, approximately 12 hours after the last iv dose, to ensure the subjects continued to receive uninterrupted daily therapy.
To facilitate study enrollment at all times of the day infusion times were adjusted up to ± 2 hours per infusion interval until the desired administration schedule was achieved.

Background therapy: -

Evidence for comparator:

The comparator drug, linezolid, is approved worldwide for the treatment of ABSSSI caused by Gram positive pathogens and has an acceptable and well defined safety profile. Linezolid can be administered iv and po and has regulatory approval for the treatment of ABSSSI caused by Gram positive pathogens including MRSA.

Actual start date of recruitment	22 June 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	Poland: 6
Country: Number of subjects enrolled	Romania: 49
Country: Number of subjects enrolled	Croatia: 18
Country: Number of subjects enrolled	Bulgaria: 49
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Latvia: 31
Country: Number of subjects enrolled	United States: 415
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 55
Worldwide total number of subjects	655
EEA total number of subjects	173

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	580
From 65 to 84 years	67
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The study is designed to enrolled adult patients with ABSSSI that was known or suspected to be due to a Gram positive pathogen(s). Subject randomization was stratified across treatment groups by type of infection (wound infection, cellulitis/erysipelas, and major abscess) and geographic region.

Pre-assignment

Screening details:

Subjects who met inclusion criteria and did not meet exclusion criteria were randomly assigned to a treatment group, and received their first dose of test article within 4 hours after randomization. All subjects were expected to present with ABSSSI severe enough to require a minimum of at least 3 days of i.v. treatment.

Period 1

Period 1 title	Treatment period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Treatment phase (both iv and po) of the study was double blind and double-dummy.
In an effort to maintain blinding, each site employed shrouding of the iv bag and iv lines used for infusion of test article. To maintain double-blinding, subjects on both arms received the same number of tablets (3 tablets in the morning [1 of which was over-encapsulated] and 1 over encapsulated tablet in the evening).

Arms

Are arms mutually exclusive?	Yes
Arm title	Omadacycline

Arm description:

Investigational therapy: omadacycline 100 mg i.v. q12h (2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg p.o. q24h after a minimum of 3 days (6 doses) of i.v. treatment, thus 6 overall IV doses because of the blinding. For subjects assigned to OMC, they received 4 active doses plus 2 placebo doses to keep the blinded. Total treatment duration of 7 to 14 days.

Arm type	Experimental
Investigational medicinal product name	Omadacycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

2 doses of Omadacycline (100 mg) iv every 12 hours, followed by 100 mg iv every 24 hours, with the option to switch 300 mg po every 24 hours.

Arm title	Linezolid

Arm description:

Reference therapy: linezolid, 600 mg iv q12h with the option to switch to 600 mg po q12h after a minimum of 3 days (6 doses) of iv treatment. Total treatment duration of 7 to 14 days.

Arm type	Active comparator
Investigational medicinal product name	Linezolid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
600 mg Linezolid iv every 12 hours with the option to switch to 600 mg po every 12 hours.

Number of subjects in period 1	Omadacycline	Linezolid
Started	329	326
Completed	301	294
Not completed	28	32
randomized but not treated	7	-
Consent withdrawn by subject	9	4
Physician decision	1	1
death	1	2
Adverse event, non-fatal	-	1
premature discontinuation	-	6
Lost to follow-up	10	18

Baseline characteristics

Reporting groups

Reporting group title	Treatment period 1

Reporting group description: -

Reporting group values	Treatment period 1	Total	
Number of subjects	655	655	
Age categorical Units: Subjects			
Adults (18-64 years)	580	580	
From 65-84 years	67	67	
85 years and over	8	8	
Gender categorical Units: Subjects			
Female	232	232	
Male	423	423	

Subject analysis sets

Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population consisted of all randomized subjects regardless of whether or not the subject received test article. A total of 655 subjects were randomized (329 subjects in the omadacycline group and 326 subjects in the linezolid group) in the study.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all randomized subjects who received test article. All safety analyses were conducted in this analysis set.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population consisted of all randomized subjects without a baseline sole Gram negative ABSSSI pathogen.

Reporting group values	Intent-to-Treat Population	Safety population	mITT
Number of subjects	655	645	627
Age categorical Units: Subjects			
Adults (18-64 years)	580	570	
From 65-84 years	67	67	
85 years and over	8	8	
Gender categorical Units: Subjects			
Female		229	
Male		416	

End points

End points reporting groups

Reporting group title	Omadacycline

Reporting group description:

Investigational therapy: omadacycline 100 mg i.v. q12h (2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg p.o. q24h after a minimum of 3 days (6 doses) of i.v. treatment, thus 6 overall IV doses because of the blinding. For subjects assigned to OMC, they received 4 active doses plus 2 placebo doses to keep the blinded. Total treatment duration of 7 to 14 days.

Reporting group title	Linezolid

Reporting group description:

Reference therapy: linezolid, 600 mg iv q12h with the option to switch to 600 mg po q12h after a minimum of 3 days (6 doses) of iv treatment. Total treatment duration of 7 to 14 days.

Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population consisted of all randomized subjects regardless of whether or not the subject received test article. A total of 655 subjects were randomized (329 subjects in the omadacycline group and 326 subjects in the linezolid group) in the study.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all randomized subjects who received test article. All safety analyses were conducted in this analysis set.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population consisted of all randomized subjects without a baseline sole Gram negative ABSSSI pathogen.

Primary: Overall Clinical Response at PTE Visit Based on Investigator Assessments

End point title	Overall Clinical Response at PTE Visit Based on Investigator Assessments

End point description:

Overall clinical response at Post Treatment Evaluation was based on the investigator assessment at the EOT and Post Treatment Evaluation visits. Clinical success at the Early clinical Response (ECR) assessment was defined as reduction of the size of the primary lesion ≥ 20% compared to Screening measurement.

End point type	Primary

End point timeframe:

Post Treatment Evaluation (PTE) visit was conducted 7 to 14 days after the subject's last day of therapy. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days.

End point values	Omadacycline	Linezolid	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	311	627	
Units: Number of subjects analysed				
Clinical success	272	260	532	
Clinical failure	20	27	47	
Indeterminate	24	24	48	

Statistical analyses

Statistical analysis title	SAS Version 9.3 (or higher)

Statistical analysis description:

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SD), medians, minimums, and maximums for continuous variables were provided. All comparisons were for omadacycline versus linezolid.

Comparison groups	Omadacycline v Linezolid
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Median difference (net)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	8.2
Variability estimate	Standard deviation

Notes:

[1] - The study was designed to show non-inferiority in the primary efficacy outcome as clinical response at PTE was based on the investigator assessment at the EOT and PTE visits. An non inferiority margin of 10% was used for the analysis in the mITT population. To test the null hypothesis, a 2-sided 95% confidence interval (CI) was constructed based on the Miettinen and Nurminen method without stratification.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed from the signing of ICF to the time of the Final Follow-up assessment.	
Adverse event reporting additional description:	
Safety assessments included clinical review of reported adverse events, serious AEs (SAEs).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Omadacycline
Reporting group description:	
Investigational therapy: omadacycline 100 mg iv q12h (2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg po q24h after a minimum of 3 days (6 doses) of iv treatment. For subjects assigned to OMC, they received 4 active doses plus 2 placebo doses to keep the blinded. Total treatment duration of 7 to 14 days.	
Reporting group title	Linezolid
Reporting group description:	
Reference therapy: linezolid, 600 mg iv q12h with the option to switch to 600 mg po q12h after a minimum of 3 days (6 doses) of iv treatment. Total treatment duration of 7 to 14 days.	

Serious adverse events	Omadacycline	Linezolid	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 323 (3.72%)	8 / 322 (2.48%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 323 (0.31%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 323 (0.31%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 323 (0.31%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			

subjects affected / exposed	0 / 323 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 323 (0.62%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteremia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 323 (0.31%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 323 (0.62%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 323 (0.62%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Omadacycline	Linezolid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 323 (43.65%)	139 / 322 (43.17%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 323 (2.79%)	14 / 322 (4.35%)	
occurrences (all)	156	147	
AST increased			

subjects affected / exposed	8 / 323 (2.48%)	12 / 322 (3.73%)	
occurrences (all)	156	147	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 323 (3.10%)	13 / 322 (4.04%)	
occurrences (all)	156	147	
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	28 / 323 (8.67%)	19 / 322 (5.90%)	
occurrences (all)	156	147	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	40 / 323 (12.38%)	32 / 322 (9.94%)	
occurrences (all)	386	369	
Vomiting			
subjects affected / exposed	17 / 323 (5.26%)	16 / 322 (4.97%)	
occurrences (all)	156	147	
Diarrhea			
subjects affected / exposed	7 / 323 (2.17%)	10 / 322 (3.11%)	
occurrences (all)	156	147	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 323 (2.17%)	0 / 322 (0.00%)	
occurrences (all)	156	147	
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	17 / 323 (5.26%)	19 / 322 (5.90%)	
occurrences (all)	156	147	
Cellulitis			
subjects affected / exposed	15 / 323 (4.64%)	15 / 322 (4.66%)	
occurrences (all)	156	147	
Wound infection			
subjects affected / exposed	8 / 323 (2.48%)	5 / 322 (1.55%)	
occurrences (all)	156	147	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2015	Protocol amendment 1 (dated 27 Oct 2015 and labeled as version 2). All Screening evaluations, with the exception of the blood culture, should be completed within 24 hours prior to randomization. The blood culture should be completed within 24 hours of the first dose of test article. Monoamine oxidase inhibitors were prohibited from 14 days prior to Screening through the Final Follow-up assessment. Antacids and/or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) are restricted during oral treatment. The Screening lesion size measurement must be collected within 4 hours prior to randomization. Subjects should receive their first dose of test article within 4 hours after randomization. The first oral test article dose must be administered in the morning. If bacteria are isolated from baseline blood cultures, repeat blood cultures should be collected on the day that the positive blood culture is detected. If subsequent blood cultures are also positive, repeat the blood culture as necessary until negative cultures are obtained. Additional clarification regarding the storage, dispensation, reconciliation, and monitoring of oral test article supplies was included to ensure blinding was maintained. Up to 4 blood samples for PK analysis were collected between Days 1 and 7. At the PTE visit, an infections site specimen for culture and Gram stain should be obtained for subjects who were clinical failures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported