Clinical trial results:
A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE BLIND, ACTIVE CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DELAFLOXACIN COMPARED WITH VANCOMYCIN + AZTREONAM IN PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Summary

EudraCT number	2012-001767-71
Trial protocol	HU LV ES BG HR
Global end of trial date	21 June 2014

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018
Summary attachment (see zip file)	Delafloxacin 302 JAC Manuscript (Efficacy and safety of delafloxacin compared with vancomycin plus aztreonamABSSSIJAC17.pdf)

Trial information

Trial identification

Sponsor protocol code	RX-3341-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01811732
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 76096

Notes:

Sponsors

Sponsor organisation name	Melinta Therapeutics
Sponsor organisation address	300 George Street, Suite 301, New Haven, United States, 06511
Public contact	Sue Cammarata, Melinta Therapeutics, 1 3127249401, scammarata@melinta.com
Scientific contact	Sue Cammarata, Melinta Therapeutics, 1 3127249401, scammarata@melinta.com

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	04 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2014
Global end of trial reached?	Yes
Global end of trial date	21 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical efficacy of delafloxacin compared with vancomycin + aztreonam in patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) at the Follow-up Visit (Day 14 +/- 1).

Protection of trial subjects:

This study was conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including International Conference on Harmonisation (ICH) guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Background therapy:

Patients who had received 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for treatment of the ABSSSI under study in the 14 days before study entry were limited to no more than 25% of total randomized patients.

Evidence for comparator:

The comparator selected for this study was vancomycin + aztreonam based on activity against gram-positive and gram-negative bacteria, respectively. Vancomycin is a glycopeptide antibiotic that has been in clinical use for the prophylaxis and treatment of infections caused by gram-positive bacteria for nearly 50 years. Aztreonam is a monobactam antibiotic with activity against gram-negative bacteria. Since delafloxacin has activity against both gram-positive and gram-negative pathogens and vancomycin is only active against gram-positive pathogens, aztreonam was given to patients for gram-negative coverage.

Actual start date of recruitment	15 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United States: 542
Country: Number of subjects enrolled	Israel: 24
Worldwide total number of subjects	660
EEA total number of subjects	37

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)	614
From 65 to 84 years	39
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

A total of 660 patients were enrolled at 54 global sites in Europe (118 patients) and the United States (542 patients). The first patient was enrolled on 25 April 2013, the last patient was enrolled on 10 May 2014, and the final study visit was conducted on 24 June 2014.

Pre-assignment

Screening details:

Eligibility criteria included age ≥18 years, and a diagnosis of ABSSSI, defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection with ≥75 cm2 of erythema and ≥2 signs of systemic infection.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a double-blind study. An unblinded pharmacist obtained treatment assignments and provided blinded treatment to the blinded investigator for administration to the patient. A placebo infusion was given in the same manner as aztreonam to patients receiving delafloxacin. All personnel who evaluated patient efficacy and safety were blinded, with the exception of an unblinded statistician who was responsible for generating tables for the bioanalytical staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	Delafloxacin

Arm description:

Delafloxacin Treatment Group

Arm type	Experimental
Investigational medicinal product name	Delafloxacin Powder for Solution for Intravenous Infusion
Investigational medicinal product code	RX-3341-83
Other name	ABT-492, Abbott-319492
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Delafloxacin for Injection, 300 mg/vial, is formulated as a sterile, nonpyrogenic, light yellow to tan-colored lyophilized cake. Patients received delafloxacin, 300 mg IV, every 12 hours for 10 to 28 doses. Patients randomly assigned to the delafloxacin treatment arm received a blinded placebo infusion in place of the aztreonam given to the vancomycin patients from the unblinded pharmacist or unblinded designee, which was discontinued as soon as possible if a gram-negative organism was not identified in baseline cultures.

Arm title	Vancomycin + Aztreonam

Arm description:

Vancomycin + Aztreonam Treatment Group

Arm type	Active comparator
Investigational medicinal product name	Vancomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sterile vancomycin hydrochloride was supplied as an off-white lyophilized powder containing vancomycin hydrochloride equivalent of 1 g vancomycin activity. Patients randomized to vancomycin received IV doses for the entire course of treatment. The recommended starting dose of vancomycin was 15 mg/kg based on actual body weight or as per local standard of care. All study sites were to monitor vancomycin therapeutic drug levels on Day 2 (+1 day, after at least 3 doses of study drug have been administered) and Day 6 (+/-1 day) and that adjustments in vancomycin dose be made with the intent of maintaining a minimum trough concentration of >15 ug/mL up to a maximum trough concentration of 20 ug/mL.

Investigational medicinal product name	Aztreonam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aztreonam for Injection is a sterile, nonpyrogenic, sodium-free, lyophilized, off-white to slightly yellow solid. Until a baseline culture confirmed no gram-negative pathogens, the unblinded pharmacist or unblinded designee provided a blinded infusion of aztreonam for patients in the vancomycin group and a blinded placebo infusion in place of the aztreonam for patients in the delafloxacin group. For patients in the vancomycin treatment arm the aztreonam dose was 2 g BID.

Number of subjects in period 1	Delafloxacin	Vancomycin + Aztreonam
Started	331	329
Completed	276	271
Not completed	55	58
Adverse event, serious fatal	1	1
Noncompliance with Study Drug	2	2
Randomized in error	-	1
Physician decision	2	-
Consent withdrawn by subject	15	9
Adverse event, non-fatal	3	9
Lost to follow-up	24	30
Noncompliance with Study	5	5
Lack of efficacy	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Delafloxacin
Reporting group description:	
Delafloxacin Treatment Group	
Reporting group title	Vancomycin + Aztreonam
Reporting group description:	
Vancomycin + Aztreonam Treatment Group	

Reporting group values	Delafloxacin	Vancomycin + Aztreonam	Total
Number of subjects	331	329	660
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	305	309	614
From 65-84 years	23	16	39
85 years and over	3	4	7
Age continuous			
Units: years			
arithmetic mean	46.3	45.3	
standard deviation	± 13.91	± 14.44	-
Gender categorical			
Units: Subjects			
Female	125	120	245
Male	206	209	415

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set included all patients who were randomly assigned to treatment. Patients were analyzed according to the treatment they were assigned at randomization.	
Subject analysis set title	CE
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the ITT analysis set who met criteria specified in the SAP including 1) received the correct study drug, 2) received at least 80% of expected doses, 3) had required clinical assessments at the Follow up Visit (Day 14 +/- 1 day) or patient was considered a clinical failure, 4) did not receive any concomitant systemic antibacterials, and 5) had no protocol deviations that would affect efficacy.	

Reporting group values	ITT	CE	
Number of subjects	660	484	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	614	455	
From 65-84 years	39	28	
85 years and over	7	1	
Age continuous Units: years			
arithmetic mean	45.8	46.3	
standard deviation	± 14.18	± 13.98	
Gender categorical Units: Subjects			
Female	245	165	
Male	415	319	

End points

End points reporting groups

Reporting group title	Delafloxacin
Reporting group description:	
Delafloxacin Treatment Group	
Reporting group title	Vancomycin + Aztreonam
Reporting group description:	
Vancomycin + Aztreonam Treatment Group	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set included all patients who were randomly assigned to treatment. Patients were analyzed according to the treatment they were assigned at randomization.	
Subject analysis set title	CE
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the ITT analysis set who met criteria specified in the SAP including 1) received the correct study drug, 2) received at least 80% of expected doses, 3) had required clinical assessments at the Follow up Visit (Day 14 +/- 1 day) or patient was considered a clinical failure, 4) did not receive any concomitant systemic antibacterials, and 5) had no protocol deviations that would affect efficacy.	

Primary: Investigator-Assessed Response at Follow-Up Visit

End point title	Investigator-Assessed Response at Follow-Up Visit
End point description:	
The primary efficacy endpoint for the EMA submission was the investigator-assessed response at the FU visit in the ITT analysis set. Cure was defined as the complete resolution of all baseline signs and symptoms of ABSSSI, Improved as some signs and symptoms remained but no additional antimicrobial was required (improved was counted as failure for the primary analysis), and Failure as lack of efficacy after at least 4 doses of study treatment, a treatment-related AE, antibacterial drug therapy required for more than 28 doses, and/or the need for unplanned surgical intervention after study entry except for limited bedside debridement and standard wound care.	
End point type	Primary
End point timeframe:	
Follow-up (FU) Visit (Day 14 +/- 1 day)	

End point values	Delafloxacin	Vancomycin + Aztreonam	ITT	CE
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	331	329	660	484
Units: Patients				
Cure	172	166	338	284
Failure	159	163	322	200

Statistical analyses

Statistical analysis title	Non-inferiority Hypothesis Test

Statistical analysis description:

H0: Difference (Delafloxacin treatment group minus Vancomycin + Aztreonam treatment group) of clinical cure rates ≤ -10%

Comparison groups	Delafloxacin v Vancomycin + Aztreonam
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in Cure Rate
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	9.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study drug administration to 30 days (+3) after last dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Delafloxacin
Reporting group description: -	
Reporting group title	Vancomycin + Aztreonam

Reporting group description: -

Serious adverse events	Delafloxacin	Vancomycin + Aztreonam	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 324 (3.70%)	12 / 326 (3.68%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hepatic cirrhosis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polysubstance dependence			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-Induced Mood Disorder			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (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			
Cellulitis			
subjects affected / exposed	2 / 324 (0.62%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 324 (0.31%)	2 / 326 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin bacterial infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 324 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Delafloxacin	Vancomycin + Aztreonam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 324 (47.53%)	193 / 326 (59.20%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 324 (3.70%)	10 / 326 (3.07%)	
occurrences (all)	12	10	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 324 (2.16%)	8 / 326 (2.45%)	
occurrences (all)	7	8	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 324 (3.09%)	25 / 326 (7.67%)	
occurrences (all)	11	26	
Dizziness			
subjects affected / exposed	6 / 324 (1.85%)	7 / 326 (2.15%)	
occurrences (all)	6	7	
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	28 / 324 (8.64%)	44 / 326 (13.50%)	
occurrences (all)	44	66	
Pyrexia			
subjects affected / exposed	6 / 324 (1.85%)	8 / 326 (2.45%)	
occurrences (all)	6	9	
Chills			
subjects affected / exposed	0 / 324 (0.00%)	7 / 326 (2.15%)	
occurrences (all)	0	14	
Pruritus generalised			

subjects affected / exposed	3 / 324 (0.93%)	15 / 326 (4.60%)	
occurrences (all)	3	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 324 (8.33%)	10 / 326 (3.07%)	
occurrences (all)	31	12	
Nausea			
subjects affected / exposed	24 / 324 (7.41%)	28 / 326 (8.59%)	
occurrences (all)	25	29	
Vomiting			
subjects affected / exposed	7 / 324 (2.16%)	10 / 326 (3.07%)	
occurrences (all)	7	11	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 324 (0.93%)	11 / 326 (3.37%)	
occurrences (all)	3	11	
Infections and infestations			
Infection			
subjects affected / exposed	28 / 324 (8.64%)	25 / 326 (7.67%)	
occurrences (all)	33	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2013	Changes to the protocol included an update of the sponsor name to Melinta Therapeutics from Rib-X Pharmaceuticals. An FDA secondary objective was updated to include evaluating clinical efficacy in patients with MRSA, and the EMA secondary objectives and endpoints were updated to match those of the FDA. Inclusion and exclusion criteria was clarified, and additionally, an exclusion criteria was added for patients with a history or physical examination finding of peripheral neuropathy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29029278