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

Summary

EudraCT number	2014-004983-39
Trial protocol	HU EE LV SK BG
Global end of trial date	29 January 2016

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 303 CID Manuscript (303 manuscript ciy165.Final.pdf)

Trial information

Trial identification

Sponsor protocol code	RX-3341-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01984684
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 62772, IND: 76096

Notes:

Sponsors

Sponsor organisation name	Melinta Therapeutics, Inc.
Sponsor organisation address	300 George Street, Suite 301, New Haven, United States,
Public contact	Sue Cammarata, Melinta Therapeutics, Inc, 1 3127249401, scammarata@melinta.com
Scientific contact	Sue Cammarata, Melinta Therapeutics, Inc, 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	25 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2016
Global end of trial reached?	Yes
Global end of trial date	29 January 2016
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 day)

Protection of trial subjects:

The 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 received 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for treatment of 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 in gram-positive pathogens, aztreonam was given to patients for gram-negative coverage.

Actual start date of recruitment	02 May 2014
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	Romania: 40
Country: Number of subjects enrolled	Bulgaria: 87
Country: Number of subjects enrolled	Estonia: 72
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Latvia: 51
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Georgia: 31
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Mexico: 12

Country: Number of subjects enrolled	Moldova, Republic of: 31
Country: Number of subjects enrolled	Peru: 63
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 398
Worldwide total number of subjects	850
EEA total number of subjects	276

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)	684
From 65 to 84 years	151
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

A total of 850 patients were enrolled at 76 global sites in Europe (338 patients), Asia (23 patients), Latin America (91 patients), and the US (398 patients). The first patient was enrolled on 02 May 2014 and the last patient was enrolled on 10 December 2015. and the final study visit was conducted on 29 January 2016.

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 ≥ 75cm2 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 data.

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 with a CrCl > 29 mL/min at Screening received delafloxacin, 300 mg IV, every 12 hours for 6 doses, followed by delafloxacin, 450 mg orally, every 12 hours for an additional 4 to 22 doses. Patients with a CrCl of 15 to 29 mL/min at Screening received delafloxacin, 200 mg IV, given every 12 hours for all doses; no oral study drug was given. 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 the unblinded designee, which was discontinued as soon as possible if a gram negative organism was not identified in baseline cultures.

Investigational medicinal product name	Delafloxacin Oral Tablet
Investigational medicinal product code	RX-3341-83
Other name	ABT-492, Abbott-319492
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The delafloxacin tablet formulation consisted of delafloxacin as the free acid in a traditional wet granulation of drug substance with commonly used excipients and a blend of basic buffering agents.

Patients with a CrCl > 29 mL/min at Screening received delafloxacin, 300 mg IV, every 12 hours for 6 doses, followed by delafloxacin, 450 mg orally, every 12 hours for an additional 4 to 22 doses. Patients with a CrCl of 15 to 29 mL/min at Screening received delafloxacin, 200 mg IV, every 12 hours for all doses (no oral therapy).

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. After the first 6 IV doses, patients on IV vancomycin who had a CrCl of > 29 mL/min at Screening also received oral placebo BID to maintain blinding. The recommended starting dose of vancomycin was 15 mg/kg based on actual body weight or as per local standard of care. It was recommended that study sites 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 µg/mL up to a maximum trough concentration of 20 µg/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 the 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 with a CrCl greater than 29 mL/min at Screening, the aztreonam dose was 2 g BID; for patients with a CrCl of 15 to 29 mL/min at Screening, the aztreonam dose was 1 g BID.

Number of subjects in period 1	Delafloxacin	Vancomycin + Aztreonam
Started	423	427
Completed	366	368
Not completed	57	59
Noncompliance with Study Drug	4	2
Adverse event, serious fatal	-	1
Physician decision	4	3
Consent withdrawn by subject	8	9
Adverse event, non-fatal	8	12
Lost to follow-up	25	24
Noncompliance with Study	1	-

Lack of efficacy	3	6
Protocol deviation	4	2

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	423	427	850
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)	338	346	684
From 65-84 years	79	72	151
85 years and over	6	9	15
Age continuous			
Units: years			
arithmetic mean	51.2	50.2	
standard deviation	± 15.98	± 16.03	-
Gender categorical			
Units: Subjects			
Female	161	151	312
Male	262	276	538

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, regardless of whether they received treatment or not. 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 the 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	850	682	
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)	684	541	
From 65-84 years	151	127	
85 years and over	15	14	
Age continuous Units: years			
arithmetic mean	50.7	51.9	
standard deviation	± 16.0	± 15.80	
Gender categorical Units: Subjects			
Female	312	253	
Male	538	429	

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, regardless of whether they received treatment or not. 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 the 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 (Day 14 +/- 1 day) 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 the 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	423	427	850	682
Units: Patients				
Cure	244	255	499	444
Failure	179	172	351	238

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	Vancomycin + Aztreonam v Delafloxacin
Number of subjects included in analysis	850
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in Cure Rate
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	4.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of the Informed Consent to 30 (+3) days 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	18 / 417 (4.32%)	26 / 425 (6.12%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			

subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 417 (0.24%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 417 (0.00%)	2 / 425 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
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			
Acute respiratory failure			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (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	2 / 417 (0.48%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 417 (0.00%)	2 / 425 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			

subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 417 (0.24%)	3 / 425 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 417 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 417 (0.24%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 417 (0.24%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 417 (0.24%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	4 / 417 (0.96%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 4	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	182 / 417 (43.65%)	167 / 425 (39.29%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 417 (1.20%)	10 / 425 (2.35%)	
occurrences (all)	5	11	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 417 (3.36%)	16 / 425 (3.76%)	
occurrences (all)	15	19	
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	13 / 417 (3.12%)	10 / 425 (2.35%)	
occurrences (all)	19	13	
Pyrexia			
subjects affected / exposed	11 / 417 (2.64%)	9 / 425 (2.12%)	
occurrences (all)	12	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	32 / 417 (7.67%)	14 / 425 (3.29%)	
occurrences (all)	34	14	
Nausea			
subjects affected / exposed	32 / 417 (7.67%)	19 / 425 (4.47%)	
occurrences (all)	36	20	
Vomiting			
subjects affected / exposed	10 / 417 (2.40%)	8 / 425 (1.88%)	
occurrences (all)	10	8	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 417 (0.96%)	9 / 425 (2.12%)	
occurrences (all)	4	9	
Infections and infestations			
Infection			
subjects affected / exposed	16 / 417 (3.84%)	15 / 425 (3.53%)	
occurrences (all)	26	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	Amendment 1 was country specific applying only to study sites in Korea. The medical monitor was updated to Sue Cammarata, M.D. from Eugene Sun, M.D. It was added that for patients in the vancomycin treatment arm, vancomycin dose adjustments for impaired renal function will be allowed, and it was also added that patients with a CrCl of 15 - 29 mL/min at Screening may receive 1 gram of aztreonam every 12 hours. Patients receiving initial combination therapy with aztreonam with CrCl greater than 29 mL/min at Screening will receive 2 grams every 12 hours.
09 May 2014	Changes to the protocol amendment included a statement that vancomycin dosing and monitoring as described in the protocol were a recommendation, not required, and that sites could elect to dose patients in accordance with local standard of care. In addition, PK sample time points on Day 5 were removed and blood sample collections on Day 3 were updated to 1.5 and 3 hours only. Monitoring of glucose on select days and pharmacoeconomic endpoints were removed. Pain assessments were to be made by paper patient reported instead of electronically, and anaerobic blood cultures were optional for sites that were unable to process. A modification was made that abscesses, and no other infection type, were to be stratified by treatment group. Finally, a clarification was made that CrCl was to be calculated with each blood chemistry panel, and concomitant medications were to be recorded starting at the time of first study drug dose instead of from the time of informed consent.
06 April 2015	Changes to the protocol included removing a secondary objective for the FDA of clinical response of reduction of erythema of >=30% at 48 - 72 hours. For patients that withdrew and did not complete study treatment and receive other antibiotics, procedures were updated to not collect follow-up efficacy data. The update was made that digital photography and manual measurements made on Day 3 were to be collected within 2 hours before each dose and did not have to be 12 hours apart. A targeted physical examination was added to End of Treatment patients discontinuing prematurely from study treatment. A +3-day window was added to the Telephone Call Follow-up, and if a patient was positive for Hepatitis B or C at screening, it should be added to the medical history section of the eCRF as a pre-existing condition. An update to the delafloxacin dosing regimen was made that dose would not be modified based on CrCl levels as screening. The percentage of patients with a BMI of >=30 was increased to 40% of the total population and no more than 30% of enrolled patients would have wound infections. Secondary efficacy endpoints were updated and were to be tested using a fixed sequential procedure, and end of treatment was added to database for visits with the clinical response. Finally, administration of nonstudy antibacterials for treatment-related AE was included in clinical response definition of failure, and once a patient was considered failure at a particular visit, the patient was considered a failure at all later timepoints.
03 June 2015	This protocol amendment included changes to the dosing of delafloxacin based on CrCl levels, and specified that patients with a BMI of >=30 were to make up no more than 50% of the enrolled population. Treatment differences reported for the primary and secondary endpoints from updated from vancomyin - delafloxacin to delafloxacin - vancomycin. Lastly, it was added that the sensitivity analyses of the primary endpoints were to be stratified by BMI (<30 and >=30).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29518178