Clinical trial results:
A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, COMPARATOR-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS TO ORAL DELAFLOXACIN IN ADULT SUBJECTS WITH COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

Summary

EudraCT number	2015-003026-14
Trial protocol	HU ES LV BG DE SI PL
Global end of trial date	07 August 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2020
First version publication date	01 March 2020
Summary attachment (see zip file)	A Phase 3 Study to Compare Delafloxacin With Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP) (Horcajada et al CABP publication_2019.pdf)

Trial information

Trial identification

Sponsor protocol code	ML-3341-306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02679573
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Melinta Therapeutics, Inc.
Sponsor organisation address	44 Whippany Rd, Suite 280, Morristown, NJ, United States, 07960
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	15 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2018
Global end of trial reached?	Yes
Global end of trial date	07 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to to assess the clinical efficacy of intravenous (IV) and oral delafloxacin in adult subjects with Community Acquired Bacterial Pneumonia (CABP) at 5 to 10 days after the last dose of study drug (Test-of-Cure visit, TOC) compared to IV and oral comparator in the Intent-to-Treat (ITT) population.

Protection of trial subjects:

The study was conducted in compliance with the protocol and all regulatory requirements, in accordance with Good Clinical Practice (GCP), including International Council for Harmonisation (ICH) guidelines, and was in general conformity with the most recent version of the Declaration of Helsinki.

Background therapy:

None.

Evidence for comparator:

Moxifloxacin 400 mg IV or oral once daily was the recommended dosage in treatment of patients with CABP. Moxifloxacin has the antibacterial coverage to treat the range of gram-positive and gram-negative pathogens seen in CABP such as Streptococcus pneumoniae and Haemophilus influenzae as well as atypical pathogens. At the investigator’s discretion, in patients with confirmed infection due to methicillin-resistant Staphylococcus aureus (MRSA), IV linezolid could be substituted for moxifloxacin. Linezolid is approved for treatment of CABP at a dose of 600 mg BID. Linezolid is one of the currently recommended treatments for patients with confirmed MRSA infections.

Actual start date of recruitment	14 December 2016
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	Poland: 28
Country: Number of subjects enrolled	Romania: 59
Country: Number of subjects enrolled	Slovenia: 15
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Bulgaria: 58
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Latvia: 40

Country: Number of subjects enrolled	Argentina: 20
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Dominican Republic: 2
Country: Number of subjects enrolled	Georgia: 95
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	Serbia: 142
Country: Number of subjects enrolled	South Africa: 71
Country: Number of subjects enrolled	Ukraine: 168
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	859
EEA total number of subjects	251

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)	477
From 65 to 84 years	354
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

A total of 859 patients were enrolled as part of the ITT population at 86 centers in Western and Eastern Europe, South Africa, Latin America, and the United States. The first patient was enrolled on 14 December 2016, the last patient was enrolled on 13 July 2018, and the final study visit was conducted on 07 August 2018.

Pre-assignment

Screening details:

Patients 18 years and older were screened for baseline chest radiography with evidence of CABP, clinical signs and symptoms of CABP, and Pneumonia Patient Outcomes Research Team (PORT) Risk Class II, III, IV, or V. A total of 937 patients were screened and 77 subjects screen failed due to meeting exclusion or failing to meet inclusion criteria.

Period 1

Period 1 title	Overall Trial (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:

An unblinded pharmacist obtained treatment assignments and provided blinded treatment to the blinded investigator for administration. A placebo infusion was given in the same manner as moxifloxacin once daily to patients receiving delafloxacin. All personnel evaluating efficacy and safety were blinded, except for an unblinded statistician who generated tables for the bioanalytical an dosing data. For oral dosing, placebo tablets were used similarly to maintain the blind between groups.

Arms

Are arms mutually exclusive?	Yes
Arm title	Delafloxacin

Arm description:

Delafloxacin 300 mg was administered as a 1-hour IV infusion BID (± 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID (± 2 hours) for the remaining doses.

Arm type	Experimental
Investigational medicinal product name	Delafloxacin Powder 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:

Subjects randomized to delafloxacin received intravenous (IV) product, 300 mg every 12 hours (BID), with an option to switch to oral product, 450 mg BID. Subjects that switched to oral delafloxacin, 450 mg BID, also received oral moxifloxacin placebo QD. Delafloxacin for Injection, 300 mg/vial, was a light-yellow to tan colored lyophilized powder provided in a 20-mL clear borosilicate glass vial. A single vial of delafloxacin was reconstituted and diluted in 250 mL bags of D5W as described in the pharmacy manual.

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:

Subjects randomized to delafloxacin received intravenous (IV) product, 300 mg every 12 hours (BID), with an option to switch to oral product, 450 mg BID. Subjects that switched to oral delafloxacin, 450

mg BID, also received oral moxifloxacin placebo QD. Oral delafloxacin tablets are capsule-shaped tablets, beige with tan spots.

Arm title	Moxifloxacin

Arm description:

Moxifloxacin 400 mg was administered as a 1 hour IV infusion every 24 (± 2) hours for a minimum of 3 active doses, with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 (± 2) hours for the remaining doses.

Arm type	Active comparator
Investigational medicinal product name	Moxifloxacin hydrochloride for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to moxifloxacin received intravenous (IV) product, 400 mg every 24 hours (QD), for a minimum of 3 active doses with an option to switch to oral product, 400 mg BID for the remaining doses. Subjects randomized to moxifloxacin received IV placebo QD alternatively with active IV moxifloxacin to maintain the blind. Moxifloxacin hydrochloride for injection for this study was provided in ready-to-use 250 mL flexible bags containing 400 mg moxifloxacin in 0.8% sodium chloride aqueous solution.

Investigational medicinal product name	Moxifloxacin Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to moxifloxacin received intravenous (IV) product, 400 mg every 24 hours (QD), for a minimum of 3 active doses with an option to switch to oral product, 400 mg BID for the remaining doses. Subjects switched to oral moxifloxacin, 400 mg QD, received oral delafloxacin placebo BID. Oral moxifloxacin hydrochloride tablets are oblong, dull red-film-coated tablets containing 400mg of active product.

Number of subjects in period 1	Delafloxacin	Moxifloxacin
Started	431	428
Completed	394	389
Not completed	37	39
Adverse event, serious fatal	2	-
Physician decision	2	4
Consent withdrawn by subject	2	9
Adverse event, non-fatal	13	6
Lost to follow-up	-	3
Lack of efficacy	12	15
Protocol deviation	6	2

Baseline characteristics

Reporting groups	
Reporting group title	Delafloxacin
Reporting group description:	
Delafloxacin 300 mg was administered as a 1-hour IV infusion BID (± 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID (± 2 hours) for the remaining doses.	
Reporting group title	Moxifloxacin
Reporting group description:	
Moxifloxacin 400 mg was administered as a 1 hour IV infusion every 24 (± 2) hours for a minimum of 3 active doses, with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 (± 2) hours for the remaining doses.	

Reporting group values	Delafloxacin	Moxifloxacin	Total
Number of subjects	431	428	859
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)	228	249	477
From 65-84 years	186	168	354
85 years and over	17	11	28
Age continuous Units: years			
arithmetic mean	60.7	59.3	
standard deviation	± 16.1	± 16.6	-
Gender categorical Units: Subjects			
Female	180	175	355
Male	251	253	504

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-to-treat (ITT) population comprised all randomized subjects with a signed Informed consent form (ICF). Subjects were analyzed according to the treatment arm to which they were randomized.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population comprised all randomized subjects who received at least 1 dose of the study drug. Subjects were analyzed according to the treatment (delafloxacin or moxifloxacin) they received most often. If the duration of treatment was the same, then these subjects were summarized in the	

delafloxacin treatment group.

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

Subject analysis set description:

All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.

Reporting group values	ITT	Safety	modITT
Number of subjects	859	856	746
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)	477	475	386
From 65-84 years	354	354	333
85 years and over	28	27	27
Age continuous Units: years			
arithmetic mean	60.0	60.0	61.5
standard deviation	± 16.3	± 16.3	± 15.9
Gender categorical Units: Subjects			
Female	355	353	295
Male	504	503	451

End points

End points reporting groups

Reporting group title	Delafloxacin

Reporting group description:

Delafloxacin 300 mg was administered as a 1-hour IV infusion BID (± 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID (± 2 hours) for the remaining doses.

Reporting group title	Moxifloxacin

Reporting group description:

Moxifloxacin 400 mg was administered as a 1 hour IV infusion every 24 (± 2) hours for a minimum of 3 active doses, with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 (± 2) hours for the remaining doses.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population comprised all randomized subjects with a signed Informed consent form (ICF). Subjects were analyzed according to the treatment arm to which they were randomized.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population comprised all randomized subjects who received at least 1 dose of the study drug. Subjects were analyzed according to the treatment (delafloxacin or moxifloxacin) they received most often. If the duration of treatment was the same, then these subjects were summarized in the delafloxacin treatment group.

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

Subject analysis set description:

All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.

Primary: Clinical Success at Test of Cure (TOC)

End point title	Clinical Success at Test of Cure (TOC)

End point description:

The Investigator defined the clinical outcome based on the assessment of the subject's signs and symptoms of infection at TOC. The Investigator's assessment of clinical response was categorized as:
-Success - Resolution or near resolution of the symptoms of CABP present at study entry, no use of additional antimicrobial therapy, and no new symptoms.
-Failure - Symptoms of CABP present at study entry not resolved, new symptoms developed, subject died from CABP, or use of additional nonstudy antimicrobial therapy for treatment of the current CABP due to lack of efficacy. Subjects had to receive at least 4 doses of study drug by the end of Day 3 to be called a failure.
-Indeterminate/Missing - A response could not be determined because an efficacy assessment was not completed at the visit or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses were considered failures for the purpose of the ITT analysis.

End point type	Primary

End point timeframe:

Test of Cure (TOC) = 5 to 10 days after last dose

End point values	Delafloxacin	Moxifloxacin	ITT	modITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	431	428	859	746
Units: Patients	390	384	774	672

Statistical analyses

Statistical analysis title	Non-inferiority Hypothesis Test

Statistical analysis description:

The null (H0) and alternative (Ha) hypotheses tested to establish the noninferiority of delafloxacin were the following:

H0: Pd – Pm ≤ –0.1

Ha: Pd – Pm > –0.1

where Pd and Pm were the probabilities of the clinical outcome rates for delafloxacin and moxifloxacin, respectively.

Comparison groups	Delafloxacin v Moxifloxacin
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in Cure Rate
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	4.8

Secondary: Early Clinical Response (ECR) Responders

End point title	Early Clinical Response (ECR) Responders

End point description:

The following symptoms for the ECR were evaluated by the investigator on a four-point scale (absent, mild, moderate, severe): pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing). Improvement was defined as at least a 1-point improvement (decrease) from baseline to the assessment at 96 (± 24) hours after first dose of study drug (e.g., from severe to moderate).

- Responders: Improvement at 96 (± 24) hours after first dose of study drug in at least 2 of the symptoms, and no worsening of the other symptoms.
- Non-responders: Improvement was not achieved at 96 (± 24) hours after the first dose of study drug in at least 2 of the symptoms; or there was use of additional nonstudy antimicrobial therapy for treatment of the current CABP due to lack of efficacy; or the subject died from the current CABP. Indeterminate/missing assessments were mapped to nonresponders in the ITT statistical analysis.

End point type	Secondary

End point timeframe:

96 (± 24) hours - Due to the ±2-hour window for study drug administration, programmatically, 70 - 122 hours after the start date/time of first IV infusion was considered for the Early Clinical Response (ECR) timepoint.

End point values	Delafloxacin	Moxifloxacin	ITT	modITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	431	428	859	746
Units: Patients	383	381	764	660

Statistical analyses

Statistical analysis title	Noninferiority Hypothesis

Statistical analysis description:

The null (H0) and alternative (Ha) hypotheses tested to establish the noninferiority of delafloxacin were the following:

H0: Pd – Pm ≤ –0.125

Ha: Pd – Pm > –0.125

where Pd and Pm were the probabilities of the ECR for delafloxacin and moxifloxacin, respectively.

Comparison groups	Delafloxacin v Moxifloxacin
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in ECR Rate
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of the Informed Consent to Day 28 (+/- 2 days) after start of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Delafloxacin

Reporting group description:

Delafloxacin 300 mg was administered as a 1-hour IV infusion BID (± 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID (± 2 hours) for the remaining doses.

Reporting group title	Moxifloxacin

Reporting group description:

Moxifloxacin 400 mg was administered as a 1 hour IV infusion every 24 (± 2) hours for a minimum of 3 active doses, with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 (± 2) hours for the remaining doses.

Serious adverse events	Delafloxacin	Moxifloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 429 (5.36%)	20 / 427 (4.68%)	
number of deaths (all causes)	9	7	
number of deaths resulting from adverse events	9	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (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			
Sudden death			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 429 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			

subjects affected / exposed	1 / 429 (0.23%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 429 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 429 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			

subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 429 (0.70%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Septic shock			
subjects affected / exposed	3 / 429 (0.70%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 429 (0.23%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningomyelitis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Measles			

subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 427 (0.23%)	
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: 2 %

Non-serious adverse events	Delafloxacin	Moxifloxacin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 429 (9.56%)	31 / 427 (7.26%)	
Investigations			
Transaminases increased			
subjects affected / exposed	13 / 429 (3.03%)	6 / 427 (1.41%)	
occurrences (all)	13	6	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 429 (1.86%)	11 / 427 (2.58%)	
occurrences (all)	8	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 429 (4.66%)	14 / 427 (3.28%)	
occurrences (all)	21	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	• Allowed for the inclusion of PORT Risk Class V subjects in the study. • Added exclusion criterion to specify restrictions associated with use of linezolid (known uncontrolled arterial hypertension, pheochromocytoma, carcinoid thyrotoxicosis) and restrictions associated with use of moxifloxacin (lactose intolerance, lactase deficiency and glucose-galactose malabsorption). • Revised to reflect that local laboratory results should be obtained within the 24 hours prior to first dose of study drug to verify entry criteria in order to more accurately assess the subject's clinical condition at time of enrollment. • Clarified that oropharyngeal and nasopharyngeal specimens may include culture and/or PCR. • Revised to reflect C-reactive protein samples will not be collected. • Clarified that local/regional laboratory results will be used for patient care. • Clarified that systemic steroid use during the treatment period is allowed for a short duration (e.g., steroid burst). Inhaled steroids are allowed without any restriction. • Treatment regimens clarified. • Description of delafloxacin was updated to be consistent with the Investigator's Brochure. • The statistical analysis section was revised to reflect that a shift table will be not used to analyze change from baseline for physical exam findings. Worsening from baseline was to be captured as an adverse event.
29 March 2016	• Revised inclusion 2 to be consistent with draft guidance for industry, Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment: removed "or a change in the character of the sputum", separated vital sign abnormalities from the other clinical signs and lab abnormalities. • Added exclusion of medical history of significant hypersensitivity or allergic reaction to study drug excipients in the judgment of the investigator to exclusion 1. • Revised exclusion 4 to include criteria for documenting treatment failure based on clinical evidence and not pulmonary imaging alone. • Revised exclusion 12 to include exclusion of known uncorrected hypomagnesemia at study entry. • Revised the primary efficacy endpoint definition of improvement to include no worsening of any of the other CABP symptoms as described in the references provided in the draft guidance for industry document. • Modified the suggested criteria for IV to oral switch to improved stability if vital sign indices, e.g. no worsening. • Responders definition revised to include no worsening of other symptoms. • Nonresponders definition was revised to further clarify that additional antimicrobial treatment of the current CABP infection would only meet the Nonresponders definition if the reason for treatment was due to lack of efficacy. • Failure definition revised to clarify that additional antimicrobial treatment of the current CABP infection would only meet the Failure definition if the reason for treatment was due to lack of efficacy. • Indeterminate/Missing definition revised to clarify that a response could not be determined if the subject did not complete the planned course of study therapy for reason other than lack of efficacy. • Clarified that any potential sample size recalculation would be based on pooled information across the 2 treatment arms. • Added a table that included the definitions of symptom severity: absent (0 points), mild (1), moderate (2), and severe (3).

04 December 2017	•Procedures of chest radiography and clinical laboratory collection performed prior to the first dose of study drug. •All screening procedures performed in the 24 hour period prior to the first dose of study drug (unless otherwise noted). • Added serology testing for Chlamydia at Day 1, TOC, and Follow-up • In the PSI/PORT scoring appendix corrected a minor discrepancy in Temperature, added a converted value from BUN to urea, and added Risk Class to the scoring table. • Added a converted value from urea to BUN in the CURB-65 scoring appendix. • Primary and secondary objectives and endpoints, sample size calculations, populations and analyses were clarified for EMA submissions. • Clarifications were added to Inclusion 4 and Exclusions 4, 5, and 12. • Timing of vital signs was updated at all visits after first dose to clarify that they may be performed at any time, but should be consistent each day. • The window for the Day 7 (oral treatment) visit was updated from ± 1 day to + 1 Day so it would not coincide with the Day 5 (oral treatment) visit. • Procedures at EOT/TOC visits clarified that a CXR or CT scan is also required to be done only for lack of efficacy. • General references to "sputum specimens" were changed to "respiratory specimens" throughout the protocol • PK sections were updated to specify endpoints and analyses to be performed. • Post-Treatment Medications section updated to clarify which data should be recorded in the eCRF. • Adverse Events section updated to clarify the required time period to record data in the CRF and to note that progression of disease under study is not recorded as an AE. • All references to ICH guideline E6(R1): Good Clinical Practice were updated to (R2) to align with global regulatory requirements. • Abbreviations were added or exchanged for text throughout the protocol as per the List of Abbreviations. • Minor grammatical and formatting changes were made throughout the text

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/31988972