



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia

Summary

EudraCT number	2015-004782-92
Trial protocol	LV HU ES BG
Global end of trial date	02 January 2018

Results information

Result version number	v1 (current)
This version publication date	18 January 2019
First version publication date	18 January 2019

Trial information

Trial identification

Sponsor protocol code	NAB-BC-3781-3102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02813694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nabriva Therapeutics GmbH (formerly Nabriva Therapeutics AG)
Sponsor organisation address	Leberstraße 20, Vienna, Austria, 1110
Public contact	Jennifer Schranz, MD, Nabriva Therapeutics plc, +1 6109182842, Jennifer.Schranz@nabriva.com
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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	28 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2017
Global end of trial reached?	Yes
Global end of trial date	02 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The co-primary endpoints for the study were:

- Demonstrate the non-inferiority (NI) of lefamulin versus comparator with respect to the Early Clinical Response (96 ± 24 hours after the first dose of study drug) in the Intent-to-Treat (ITT) Analysis Set (FDA endpoint).
- Demonstrate the NI of lefamulin versus comparator with respect to the Investigator's Assessment of Clinical Response at Test of Cure (TOC) (i.e., 5-10 days after the last dose of study drug) in the modified-ITT (mITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets (EMA endpoint).

Protection of trial subjects:

This clinical study was conducted in compliance with the protocol, ethical principles that have their origin in the Declaration of Helsinki in its revised edition, the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), European Union (EU) Clinical Trials Directive 2001/20/EC, EU Commission Directive 2005/28/EC, and Code of Federal Regulation Title 21, Parts 50, 56 and 312, designated Standard Operating Procedures, and with local laws and regulations in the country of conduct. The study protocol and amendments were reviewed and approved by an IEC/IRB before conduct of the study at each participating site.

Background therapy: -

Evidence for comparator:

Moxifloxacin was chosen as the active comparator for multiple reasons. Consensus guidelines on the management of CAP in adults recommend a respiratory fluoroquinolone as an appropriate option for hospitalized patients admitted to a general ward, for outpatients with certain comorbid conditions, outpatients who have used antimicrobials in the previous few months, and outpatients in regions with high rates of macrolide-resistant *S. pneumoniae* regardless of co-morbidities or prior antibiotic use. The European Society of Clinical Microbiology and Infectious Diseases also supports the use of fluoroquinolones for outpatient treatment of CAP in areas with increased bacterial resistance rates to tetracyclines and macrolides, as well as for empiric therapy on hospitalized patients with CAP. Moxifloxacin has established efficacy against the primary CAP pathogens, and is globally available in an oral formulation, which made it a suitable comparator in this study. Moreover, moxifloxacin does not require dose adjustment in patients with renal impairment.

Actual start date of recruitment	31 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 80
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Poland: 7

Country: Number of subjects enrolled	Ukraine: 128
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Peru: 51
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Philippines: 71
Country: Number of subjects enrolled	South Africa: 55
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Georgia: 41
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	Serbia: 129
Worldwide total number of subjects	738
EEA total number of subjects	137

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)	461
From 65 to 84 years	260
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

The study was designed to enroll adults with CABP who were eligible for oral therapy. Subjects with a PORT score of II, III and IV were eligible. The first subject was randomized in August 2016 and the last subject was randomized in December 2017.

Pre-assignment

Screening details:

Subjects who met inclusion criteria and did not meet exclusion criteria were randomly assigned to a treatment group. Administration of study drug was expected to occur as soon as possible after the diagnosis of CABP with all Screening/Baseline assessments expected to be completed within 24 hours before the first dose of oral study drug.

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

Blinding implementation details:

This was a double-blind, double-dummy study. Oral formulations were provided in blister packs and all oral study medication administration utilized a "double-dummy" technique.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lefamulin

Arm description:

Lefamulin 600 mg PO q12h for 5 days (10 doses) plus moxifloxacin placebo PO q24h for 7 days (7 doses).

Arm type	Experimental
Investigational medicinal product name	Lefamulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lefamulin 600 mg PO q12h for 5 days (10 doses).

Moxifloxacin placebo PO q24h for 7 days (7 doses).

Arm title	Moxifloxacin
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Arm description:

Moxifloxacin 400 mg PO q24h for 7 days (7 doses) plus lefamulin placebo PO q12h for 5 days (10 doses).

Arm type	Active comparator
Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Moxifloxacin 400 mg PO q24h for 7 days (7 doses)

Lefamulin placebo PO q12h for 5 days (10 doses)

Number of subjects in period 1	Lefamulin	Moxifloxacin
Started	370	368
Completed	353	354
Not completed	17	14
Adverse event, serious fatal	3	3
Consent withdrawn by subject	10	9
Physician decision	-	1
Randomized but not treated	2	-
Other	1	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Lefamulin
Reporting group description: Lefamulin 600 mg PO q12h for 5 days (10 doses) plus moxifloxacin placebo PO q24h for 7 days (7 doses).	
Reporting group title	Moxifloxacin
Reporting group description: Moxifloxacin 400 mg PO q24h for 7 days (7 doses) plus lefamulin placebo PO q12h for 5 days (10 doses).	

Reporting group values	Lefamulin	Moxifloxacin	Total
Number of subjects	370	368	738
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)	234	227	461
From 65-84 years	126	134	260
85 years and over	10	7	17
Age continuous			
Units: years			
arithmetic mean	57.4	57.7	-
standard deviation	± 16.4	± 16.2	
Gender categorical			
Units: Subjects			
Female	207	180	387
Male	163	188	351

Subject analysis sets

Subject analysis set title	Intent-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Analysis Set comprised all randomized subjects regardless of whether or not the subject received study drug. A subject was considered randomized when an IRT-generated randomization number was assigned.	
Subject analysis set title	mITT Analysis Set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT Analysis Set comprised all randomized subjects who received any amount of study drug. Subjects were analyzed based on the randomized (ie, assigned) treatment group.	
Subject analysis set title	Clinically Evaluable at TOC (CE-TOC) Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The CE-TOC Analysis Set comprised all subjects who completed the TOC Visit 5 to 10 days after the last dose of study drug, unless the subject was considered a failure at the EOT Visit based on the IACR, and had no confounding factors that affected the assessment of efficacy.

Reporting group values	Intent-to-Treat (ITT) Analysis Set	mITT Analysis Set	Clinically Evaluable at TOC (CE-TOC) Analysis Set
Number of subjects	738	736	656
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)	461	460	409
From 65-84 years	260	259	233
85 years and over	17	17	14
Age continuous Units: years			
arithmetic mean	57.5	57.5	57.7
standard deviation	± 16.3	± 16.3	± 16.0
Gender categorical Units: Subjects			
Female	387	386	349
Male	351	350	307

End points

End points reporting groups

Reporting group title	Lefamulin
Reporting group description: Lefamulin 600 mg PO q12h for 5 days (10 doses) plus moxifloxacin placebo PO q24h for 7 days (7 doses).	
Reporting group title	Moxifloxacin
Reporting group description: Moxifloxacin 400 mg PO q24h for 7 days (7 doses) plus lefamulin placebo PO q12h for 5 days (10 doses).	
Subject analysis set title	Intent-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Analysis Set comprised all randomized subjects regardless of whether or not the subject received study drug. A subject was considered randomized when an IRT-generated randomization number was assigned.	
Subject analysis set title	mITT Analysis Set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT Analysis Set comprised all randomized subjects who received any amount of study drug. Subjects were analyzed based on the randomized (ie, assigned) treatment group.	
Subject analysis set title	Clinically Evaluable at TOC (CE-TOC) Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: The CE-TOC Analysis Set comprised all subjects who completed the TOC Visit 5 to 10 days after the last dose of study drug, unless the subject was considered a failure at the EOT Visit based on the IACR, and had no confounding factors that affected the assessment of efficacy.	

Primary: EMA Co-Primary: Investigator Assessment of Clinical Response (IACR) at TOC in the mITT Analysis Set

End point title	EMA Co-Primary: Investigator Assessment of Clinical Response (IACR) at TOC in the mITT Analysis Set
End point description: The EMA co-primary endpoints were the percentages of subjects with an IACR of success at TOC in the mITT and CE-TOC Analysis Sets. Investigators assessed clinical response at the TOC visit. Subjects were classified as a success, failure, or indeterminate at TOC based on predefined definitions. Success was defined as resolution or improvement of clinical signs and symptoms such that no additional antibacterial therapy was administered for the treatment of the current episode of CABP. Subjects who had an IACR of failure at a prior visit did not have an IACR performed at TOC and were considered an IACR of failure at TOC.	
End point type	Primary
End point timeframe: The TOC visit occurred 5 to 10 days after the last dose of study drug.	

End point values	Lefamulin	Moxifloxacin	mITT Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	368	368	736	
Units: Number of patients				
Clinical Success	322	328	650	
Failure	44	32	76	
Indeterminate	2	8	10	

Statistical analyses

Statistical analysis title	mITT Statistical Analysis Plan
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Statistical analysis description:

An adjusted (for the randomization stratification factors of prior antibiotic use and PORT risk class) 2 sided 95% CI for the observed difference in IACR success rates (lefamulin group minus the moxifloxacin group) was calculated using the method of Miettinen and Nurminen with Cochran-Mantel-Haenszel weights to test the null hypothesis.

Comparison groups	Moxifloxacin v Lefamulin
Number of subjects included in analysis	736
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Risk difference (RD)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	3.1
Variability estimate	Standard error of the mean

Notes:

[1] - If the lower limit of the 95% CI for the difference in IACR success rates in the mITT and the CE-TOC Analysis Sets was greater than 10%, then the null hypothesis was rejected and the NI of lefamulin to moxifloxacin was concluded.

Primary: EMA Co-Primary: Investigator Assessment of Clinical Response at TOC in the CE-TOC Analysis Set

End point title	EMA Co-Primary: Investigator Assessment of Clinical Response at TOC in the CE-TOC Analysis Set
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End point description:

The EMA co-primary endpoints were the percentages of subjects with an IACR of success at TOC in the mITT and CE-TOC Analysis Sets.

Investigators assessed clinical response at the TOC visit. Subjects were classified as a success, failure, or indeterminate at TOC based on predefined definitions. Subjects who had an IACR of failure at a prior visit did not have an IACR performed at TOC and were considered an IACR of failure at TOC.

End point type	Primary
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End point timeframe:

The TOC visit occurred 5 to 10 days after the last dose of study drug

End point values	Lefamulin	Moxifloxacin	Clinically Evaluable at TOC (CE-TOC) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	330	326	656	
Units: Number of patients				
Clinical Success	296	305	601	
Failure	34	21	55	
Indeterminate	0	0	0	

Statistical analyses

Statistical analysis title	CE-TOC Statistical Analysis Plan
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Statistical analysis description:

An adjusted (for the randomization stratification factors of prior antibiotic use and PORT risk class) 2 sided 95% CI for the observed difference in IACR success rates (lefamulin group minus the moxifloxacin group) was calculated using the method of Miettinen and Nurminen with Cochran-Mantel-Haenszel weights to test the null hypothesis.

Comparison groups	Moxifloxacin v Lefamulin
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Risk difference (RD)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	0.5
Variability estimate	Standard error of the mean

Notes:

[2] - If the lower limit of the 95% CI for the difference in IACR success rates in the mITT and the CE-TOC Analysis Sets was greater than 10%, then the null hypothesis was rejected and the NI of lefamulin to moxifloxacin was concluded.

Primary: FDA Primary: Early Clinical Response (ECR) at 96 ± 24 hours After the First Dose of Study Drug in the ITT Analysis Set

End point title	FDA Primary: Early Clinical Response (ECR) at 96 ± 24 hours After the First Dose of Study Drug in the ITT Analysis Set
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End point description:

The FDA primary endpoint was the percentage of subjects with an ECR of responder at 96 ±24 hours after the first dose of study drug in the ITT Analysis Set. Subjects were programmatically defined as a responder, non responder, or indeterminate based on CABP signs and symptoms, concomitant antibiotic use, and vital status.

End point type	Primary
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End point timeframe:

ECR was assessed 96 ±24 hours after the first dose of study drug.

End point values	Lefamulin	Moxifloxacin	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	370	368	738	
Units: Number of patients				
Clinical Success	336	334	670	
Failure	29	31	60	
Indeterminate	5	3	8	

Statistical analyses

Statistical analysis title	ITT Statistical Analysis Plan
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Statistical analysis description:

The non-inferiority (NI) test was a 1 sided hypothesis test performed at the 2.5% level of significance. This was based on the lower limit of the 2 sided 95% confidence interval (CI) for the observed difference in ECR responder rates (lefamulin group minus moxifloxacin group). The CI was calculated using an unadjusted continuity corrected Z test.

Comparison groups	Moxifloxacin v Lefamulin
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.5
Variability estimate	Standard error of the mean

Notes:

[3] - If the lower limit of the 95% CI for the difference in ECR responder rates in the ITT Analysis Set was greater than 10%, then the null hypothesis would be rejected and the NI of lefamulin to moxifloxacin would be concluded.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of informed consent to the TOC Visit. Serious adverse events were recorded from the time of informed consent to the LFU Visit.

Adverse event reporting additional description:

Subjects were evaluated for adverse events at each study visit. Questions were posed in a non leading manner so as not to bias the response. In addition to specific questioning, subjects were encouraged to spontaneously report adverse events. Adverse events were recorded whether or not they were considered to be study drug related.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Lefamulin
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Reporting group description:

The Safety Analysis Set comprised all randomized subjects who received any amount of study drug. Subjects were analyzed based on the study drug actually received. All safety analyses were conducted in this population.

Reporting group title	Moxifloxacin
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Reporting group description:

The Safety Analysis Set comprised all randomized subjects who received any amount of study drug. Subjects were analyzed based on the study drug actually received. All safety analyses were conducted in this population.

Serious adverse events	Lefamulin	Moxifloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 368 (4.62%)	19 / 368 (5.16%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events	5	3	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nuclear magnetic resonance imaging brain abnormal			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Acute myeloid leukemia			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 368 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (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 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cerebrovascular accident			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolitic stroke			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
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			
Anaemia			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Inguinal hernia strangulated			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
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 distress syndrome			
subjects affected / exposed	2 / 368 (0.54%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			

subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
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	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Empyema			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 368 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	4 / 368 (1.09%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 368 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous pleurisy			
subjects affected / exposed	0 / 368 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 368 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lefamulin	Moxifloxacin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 368 (17.39%)	11 / 368 (2.99%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	45 / 368 (12.23%)	4 / 368 (1.09%)	
occurrences (all)	48	4	
Nausea			
subjects affected / exposed	19 / 368 (5.16%)	7 / 368 (1.90%)	
occurrences (all)	19	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2016	Amendment 1 addresses revisions to the protocol requested by the US Food and Drug Administration (FDA) with respect to the non-inferiority margin. The change in the non-inferiority margin resulted in the change of other statistical parameters including the randomization ratio and sample size. FDA also requested an increase in the number of subjects with a PORT Risk Class of III or IV; methicillin-resistant Staphylococcus aureus (MRSA) to be added to the list of pathogens that would exclude study eligibility; and increase in the number of pharmacokinetic sampling time points.
17 March 2016	Amendment 2 addresses an inconsistency within the protocol regarding the use of strong P-glycoprotein inhibitors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported