



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC 3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia

Summary

EudraCT number	2014-005169-63
Trial protocol	NL HU LV PL BG
Global end of trial date	12 May 2017

Results information

Result version number	v2 (current)
This version publication date	16 December 2018
First version publication date	18 July 2018
Version creation reason	New data added to full data set Re-submission of the CSR has been made.

Trial information

Trial identification

Sponsor protocol code	NAB-BC-3781-3101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02559310
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
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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	17 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2017
Global end of trial reached?	Yes
Global end of trial date	12 May 2017
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 (with or without adjunctive linezolid) was chosen as the active comparator for multiple reasons. Consensus guidelines on the management of CABP in adults recommend a respiratory fluoroquinolone as an appropriate option for hospitalized patients admitted to a general ward. Moxifloxacin has established efficacy against the primary CABP pathogens, and is globally available in both IV and oral formulations, which made it a suitable comparator in this study. Moreover, moxifloxacin does not require dose adjustment in patients with renal impairment.

Consensus guidelines also recommend the use of adjunctive linezolid for suspected MRSA. Therefore, linezolid was to be added to the moxifloxacin group and linezolid placebo was to be added to the lefamulin group if the Investigator determined that MRSA was a probable pathogen at Screening. Similar to moxifloxacin, linezolid is available in IV and oral formulations, and does not require dose adjustment in patients with renal impairment.

Actual start date of recruitment	23 February 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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 11

Country: Number of subjects enrolled	Bulgaria: 123
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Latvia: 28
Country: Number of subjects enrolled	Bosnia and Herzegovina: 25
Country: Number of subjects enrolled	Georgia: 54
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Serbia: 57
Country: Number of subjects enrolled	Ukraine: 116
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Philippines: 40
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Thailand: 1
Worldwide total number of subjects	551
EEA total number of subjects	193

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)	311
From 65 to 84 years	214
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

The study was designed to enroll adults with CABP that was severe enough to require a minimum of at least 3 days of IV treatment. Subjects with a PORT score of III, IV and V were eligible. The first subject was randomized in February 2016 and the last subject was randomized in April 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 IV 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

Blinding implementation details:

This was a double-blind, double-dummy study. Blinding of IV lefamulin, moxifloxacin, linezolid and matching placebo was achieved using a bag cover and IV tubing cover. Intravenous infusions were administered by unblinded site personnel at a controlled rate (over approximately 60 minutes). 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 150 mg IV q12h with option to switch to 600 mg PO q12h after at least 3 days (6 doses) of IV treatment. Linezolid placebo q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.

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

Dosage and administration details:

Lefamulin 150 mg IV q12h with option to switch to 600 mg PO q12h after at least 3 days (6 doses) of IV treatment. Linezolid placebo q12h was added at baseline for patients with suspected MRSA.

Arm title	Moxifloxacin ± Linezolid for suspected MRSA
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Arm description:

Moxifloxacin 400 mg IV q24h with option to switch to 400 mg PO q24h after at least 3 days (6 doses) of IV treatment. Linezolid 600 mg IV q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.

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

Dosage and administration details:

Moxifloxacin 400 mg IV q24h with option to switch to 400 mg PO q24h after at least 3 days (6 doses) of IV treatment. Linezolid 600 mg IV q12h was added at baseline for patients with suspected MRSA.

Investigational medicinal product name	Linezolid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects in the moxifloxacin arm with suspected MRSA at baseline were to receive adjunctive Linezolid 600 mg IV q12h (or linezolid placebo in the lefamulin arm). Linezolid treatment was to be continued only in the presence of a microbiological culture confirming the presence of MRSA. If cultures did not grow MRSA, linezolid (or linezolid placebo) was to be discontinued and subjects were to be discontinued on moxifloxacin. Subjects could continue on lefamulin therapy. If linezolid was given for at least 3 days (6 doses) the Investigator had the option to switch to linezolid 600mg PO q12h.

Number of subjects in period 1	Lefamulin	Moxifloxacin ± Linezolid for suspected MRSA
Started	276	275
Completed	249	256
Not completed	27	19
Adverse event, serious fatal	4	3
Consent withdrawn by subject	13	9
Physician decision	2	1
Randomized but not treated	3	2
Lost to follow-up	5	3
Sponsor decision	-	1

Baseline characteristics

Reporting groups

Reporting group title	Lefamulin
Reporting group description: Lefamulin 150 mg IV q12h with option to switch to 600 mg PO q12h after at least 3 days (6 doses) of IV treatment. Linezolid placebo q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.	
Reporting group title	Moxifloxacin ± Linezolid for suspected MRSA
Reporting group description: Moxifloxacin 400 mg IV q24h with option to switch to 400 mg PO q24h after at least 3 days (6 doses) of IV treatment. Linezolid 600 mg IV q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.	

Reporting group values	Lefamulin	Moxifloxacin ± Linezolid for suspected MRSA	Total
Number of subjects	276	275	551
Age categorical Units: Subjects			
Adults (18-64 years)	144	167	311
From 65-84 years	116	98	214
85 years and over	16	10	26
Age continuous Units: years			
arithmetic mean	61	59.6	
standard deviation	± 16.3	± 14.9	-
Gender categorical Units: Subjects			
Female	106	115	221
Male	170	160	330

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	551	546	481
Age categorical Units: Subjects			
Adults (18-64 years)	311	307	269
From 65-84 years	214	213	189
85 years and over	26	26	23
Age continuous Units: years			
arithmetic mean	60.3	60.3	60.5
standard deviation	± 15.6	± 15.63	± 15.59
Gender categorical Units: Subjects			
Female	221	219	195
Male	330	327	286

End points

End points reporting groups

Reporting group title	Lefamulin
Reporting group description: Lefamulin 150 mg IV q12h with option to switch to 600 mg PO q12h after at least 3 days (6 doses) of IV treatment. Linezolid placebo q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.	
Reporting group title	Moxifloxacin ± Linezolid for suspected MRSA
Reporting group description: Moxifloxacin 400 mg IV q24h with option to switch to 400 mg PO q24h after at least 3 days (6 doses) of IV treatment. Linezolid 600 mg IV q12h was added at baseline for patients with suspected MRSA. The total duration of study treatment was 7 to 10 days.	
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: Early Clinical Response (ECR) at 96 ± 24 hours After the First Dose of Study Drug in the ITT Analysis Set

End point title	Early Clinical Response (ECR) at 96 ± 24 hours After the First Dose of Study Drug in the ITT Analysis Set
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
End point timeframe: ECR was assessed 96 ±24 hours after the first dose of study drug.	

End point values	Lefamulin	Moxifloxacin ± Linezolid for suspected MRSA	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	276	275	551	
Units: Number of patients				
Clinical Success	241	248	489	

Failure	29	21	50	
Indeterminate	6	6	12	

Statistical analyses

Statistical analysis title	ITT Statistical Analysis Plan
Statistical analysis description:	
A 2 sided 95% CI for the observed difference in ECR responder rates (lefamulin group minus the moxifloxacin group) was calculated to test the null hypothesis in ITT Analysis Set. If the lower limit of the 95% CI for the difference in ECR responder rates in the ITT Analysis Set was greater than 12.5%, then the null hypothesis was rejected and the NI of lefamulin to moxifloxacin was concluded.	
Comparison groups	Moxifloxacin ± Linezolid for suspected MRSA v Lefamulin
Number of subjects included in analysis	551
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	2.8
Variability estimate	Standard deviation

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

End point title	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 ± Linezolid for suspected MRSA	mITT Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	273	273	546	
Units: Number of patients				
Clinical Success	223	230	453	
Failure	43	40	83	
Indeterminate	7	3	10	

Statistical analyses

Statistical analysis title	mITT Statistical Analysis Plan
Statistical analysis description:	
A 2 sided 95% CI adjusted for the randomization stratification factors of prior antibiotic use and PORT risk class for the observed difference in IACR success rates (lefamulin group minus the moxifloxacin group) was calculated to test the null hypothesis in the mITT and CE TOC Analysis Sets.	
Comparison groups	Moxifloxacin ± Linezolid for suspected MRSA v Lefamulin
Number of subjects included in analysis	546
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	3.9
Variability estimate	Standard deviation

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

End point title	Investigator Assessment of Clinical Response at TOC in the CE-TOC 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. 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 ± Linezolid for suspected MRSA	Clinically Evaluable at TOC (CE-TOC) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	236	245	481	
Units: Number of patients				
Clinical Success	205	219	424	
Failure	31	26	57	
Indeterminate	0	0	0	

Statistical analyses

Statistical analysis title	CE-TOC Statistical Analysis Plan
Statistical analysis description:	
A 2 sided 95% CI adjusted for the randomization stratification factors of prior antibiotic use and PORT risk class for the observed difference in IACR success rates (lefamulin group minus the moxifloxacin group) was calculated to test the null hypothesis in the mITT and CE TOC Analysis Sets.	
Comparison groups	Moxifloxacin ± Linezolid for suspected MRSA v Lefamulin
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	3.4
Variability estimate	Standard deviation

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
Dictionary version	20.0

Reporting groups

Reporting group title	Lefamulin
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Reporting group description: -

Reporting group title	Moxifloxacin
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Reporting group description: -

Serious adverse events	Lefamulin	Moxifloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 273 (6.96%)	13 / 273 (4.76%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	6	5	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Increased			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (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)			
Bronchial Carcinoma			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung Neoplasm			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma of Lung			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular Seminoma (Pure)			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Shock Haemorrhagic			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
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	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiogenic Shock			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Arrhythmia			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (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			
Cerebrovascular Accident			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
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			
Death			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injection Site Reaction			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			

subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Disorder			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 273 (0.37%)	0 / 273 (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	1 / 273 (0.37%)	0 / 273 (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	1 / 273 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Necrosis			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
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			
Angioedema			
subjects affected / exposed	0 / 273 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Infectious Pleural Effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 273 (0.37%) 0 / 1 0 / 0	1 / 273 (0.37%) 0 / 1 0 / 0	
Lung Abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 273 (0.00%) 0 / 0 0 / 0	1 / 273 (0.37%) 0 / 1 0 / 0	
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 273 (1.47%) 0 / 4 0 / 1	1 / 273 (0.37%) 0 / 2 0 / 0	
Pulmonary Tuberculosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 273 (0.37%) 0 / 1 0 / 0	1 / 273 (0.37%) 0 / 1 0 / 0	
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 273 (0.37%) 0 / 1 0 / 1	0 / 273 (0.00%) 0 / 0 0 / 0	
Urinary Tract Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 273 (0.37%) 0 / 1 0 / 0	0 / 273 (0.00%) 0 / 0 0 / 0	
Viral Pharyngitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 273 (0.37%) 0 / 1 0 / 0	0 / 273 (0.00%) 0 / 0 0 / 0	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 273 (0.00%) 0 / 0 0 / 0	1 / 273 (0.37%) 0 / 1 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	105 / 273 (38.46%)	105 / 273 (38.46%)	
Investigations			
Investigations			
subjects affected / exposed	17 / 273 (6.23%)	14 / 273 (5.13%)	
occurrences (all)	32	29	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	24 / 273 (8.79%)	15 / 273 (5.49%)	
occurrences (all)	39	17	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	18 / 273 (6.59%)	37 / 273 (13.55%)	
occurrences (all)	27	49	
Diarrhoea			
subjects affected / exposed	2 / 273 (0.73%)	21 / 273 (7.69%)	
occurrences (all)	2	21	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic, and mediastinal disorders			
subjects affected / exposed	16 / 273 (5.86%)	13 / 273 (4.76%)	
occurrences (all)	16	16	
Infections and infestations			
Infections and Infestations			
subjects affected / exposed	20 / 273 (7.33%)	22 / 273 (8.06%)	
occurrences (all)	25	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2015	Addressed changes requested during the Voluntary Harmonization Procedure in Europe during assessment of the original protocol including clarification to eligibility criteria. Collection of a nasopharyngeal swab was also added.
04 March 2016	Addressed changes to the treatment duration for CABP not caused by MRSA, a decrease in the sample size, and other clarifications or corrections to align with other studies in the lefamulin clinical development program.
15 March 2016	Addressed an inconsistency within the protocol regarding the prohibited use of strong P-gp inhibitors during study participation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported