



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection due to Carbapenem-Resistant Enterobacteriaceae (CRE) Summary

EudraCT number	2013-001997-18
Trial protocol	GR ES IT DE FR
Global end of trial date	15 September 2016

#### Results information

Result version number	v1 (current)
This version publication date	27 October 2017
First version publication date	27 October 2017

#### Trial information

##### Trial identification

Sponsor protocol code	ACHN-490-007
-----------------------	--------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01970371
WHO universal trial number (UTN)	U1111-1151-2686

Notes:

#### Sponsors

Sponsor organisation name	Achaogen Inc.
Sponsor organisation address	1 Tower Pl #300, South San Francisco, United States, 94080
Public contact	Clinical Trials Registration Group, Achaogen, Inc., +1 650800-3636, clinical-trials@achaogen.com
Scientific contact	Clinical Trials Registration Group, Achaogen, Inc., +1 650800-3636, clinical-trials@achaogen.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 September 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 September 2016
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate the superiority, in terms of all-cause mortality at 28 days or significant disease-related complications, of a plazomicin-based regimen compared with a colistin-based regimen in the treatment of BSI or nosocomial pneumonia due to CRE.

Protection of trial subjects:

This study was conducted in accordance with the US Food and Drug Administration (FDA), ICH E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki (October 1996), and applicable local, state, and national laws. For European Union member states, this includes Directive 2001/20/EC, Directive 2005/28/EC, and other directives as applicable, as well as applicable local and national laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 56
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	69
EEA total number of subjects	57

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28
From 65 to 84 years	41
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 69 subjects were enrolled in the study.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1: Plazomicin

Arm description:

Subjects received 15 milligram per kilogram (mg/kg) plazomicin therapy (plus meropenem or tigecycline) as a 30-minute intravenous (IV) infusion once daily for 7 to 14 days.

Arm type	Experimental
Investigational medicinal product name	Plazomicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

15 milligrams per kilogram (mg/kg) as a 30 minute (a range of 25–50 minutes was permissible) intravenous (IV) infusion once daily. The initial dose and dosing interval were determined based on the baseline renal function. Subsequent plazomicin doses were determined based on therapeutic drug management (TDM).

Investigational medicinal product name	Meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received 2 grams (g) meropenem as a 3 hour IV infusion every 8 hours (q8h).

Investigational medicinal product name	Tigecycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received tigecycline as a 100 mg IV loading dose followed by 50 mg IV every 12 hours (q12h) as a maintenance dose. The protocol was amended to allow tigecycline to be administered as a 200 mg IV loading dose followed by 100 mg IV q12h.

<b>Arm title</b>	Cohort 1: Colistin
------------------	--------------------

Arm description:

Subjects received a 5 mg/kg IV loading dose (300 mg maximum) colistin (plus meropenem or tigecycline) followed by a 5 mg/kg/d maintenance dose divided into every 8 hours (q8h) or every 12 hours (q12h) for 7 to 14 days.

Arm type	Active comparator
----------	-------------------

Investigational medicinal product name	Colistin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received colistin in the form of its IV prodrug, colistimethate sodium (CMS), as a loading dose of colistin base activity (CBA) infused over 60 minutes. Subjects already receiving colistin at the time of enrollment and who had received  $\geq 3$  doses did not require a loading dose. Colistin dosing was adjusted according to renal function.

Investigational medicinal product name	Meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received 2 grams (g) meropenem as a 3 hour IV infusion every 8 hours (q8h).

Investigational medicinal product name	Tigecycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received tigecycline as a 100 mg IV loading dose followed by 50 mg IV every 12 hours (q12h) as a maintenance dose. The protocol was amended to allow tigecycline to be administered as a 200 mg IV loading dose followed by 100 mg IV q12h.

<b>Arm title</b>	Cohort 2: Plazomicin-Based Therapy
------------------	------------------------------------

Arm description:

Subjects received 15 mg/kg as a 30 minute IV infusion once daily. Bloodstream infection (BSI), hospital acquired bacterial pneumonia (HABP) or ventilator associated bacterial pneumonia (VABP) subjects received plazomicin and any supplemental antibiotic therapy, according to Investigator's choice, for 7 to 14 days. Complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) subjects received plazomicin monotherapy only for 4 to 7 days with an option to switch to oral therapy on or after Day 5.

Arm type	Experimental
Investigational medicinal product name	Plazomicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

15 mg/kg as a 30 minute (a range of 25–50 minutes was permissible) IV infusion once daily. The initial dose and dosing interval were determined based on the baseline renal function. Subsequent plazomicin doses were determined based on therapeutic drug management (TDM).

Number of subjects in period 1	Cohort 1: Plazomicin	Cohort 1: Colistin	Cohort 2: Plazomicin-Based Therapy
Started	18	21	30
Completed	10	8	17
Not completed	8	13	13
Death	8	13	12

Lost to follow-up	-	-	1
-------------------	---	---	---

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1: Plazomicin
-----------------------	----------------------

Reporting group description:

Subjects received 15 milligram per kilogram (mg/kg) plazomicin therapy (plus meropenem or tigecycline) as a 30-minute intravenous (IV) infusion once daily for 7 to 14 days.

Reporting group title	Cohort 1: Colistin
-----------------------	--------------------

Reporting group description:

Subjects received a 5 mg/kg IV loading dose (300 mg maximum) colistin (plus meropenem or tigecycline) followed by a 5 mg/kg/d maintenance dose divided into every 8 hours (q8h) or every 12 hours (q12h) for 7 to 14 days.

Reporting group title	Cohort 2: Plazomicin-Based Therapy
-----------------------	------------------------------------

Reporting group description:

Subjects received 15 mg/kg as a 30 minute IV infusion once daily. Bloodstream infection (BSI), hospital acquired bacterial pneumonia (HABP) or ventilator associated bacterial pneumonia (VABP) subjects received plazomicin and any supplemental antibiotic therapy, according to Investigator's choice, for 7 to 14 days. Complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) subjects received plazomicin monotherapy only for 4 to 7 days with an option to switch to oral therapy on or after Day 5.

Reporting group values	Cohort 1: Plazomicin	Cohort 1: Colistin	Cohort 2: Plazomicin-Based Therapy
Number of subjects	18	21	30
Age categorical Units: Subjects			
Adults (18-64 years)	7	9	12
From 65-84 years	11	12	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.94	63.29	62.8
standard deviation	± 13.94	± 18.25	± 18.15
Gender categorical Units: Subjects			
Female	6	11	7
Male	12	10	23

Reporting group values	Total		
Number of subjects	69		
Age categorical Units: Subjects			
Adults (18-64 years)	28		
From 65-84 years	41		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	-		
standard deviation	-		

Gender categorical			
Units: Subjects			
Female	24		
Male	45		

---

### Subject analysis sets

Subject analysis set title	Plazomicin
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK blood samples were collected on Days 1 and 4 (plus or minus 1 calendar day) from all plazomicin-treated patients for the determination of plazomicin plasma concentrations.

---

<b>Reporting group values</b>	Plazomicin		
Number of subjects	48		
Age categorical			
Units: Subjects			
Adults (18-64 years)	19		
From 65-84 years	29		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	63.6		
standard deviation	± 16.57		
Gender categorical			
Units: Subjects			
Female	13		
Male	35		

---



## End points

### End points reporting groups

Reporting group title	Cohort 1: Plazomicin
Reporting group description: Subjects received 15 milligram per kilogram (mg/kg) plazomicin therapy (plus meropenem or tigecycline) as a 30-minute intravenous (IV) infusion once daily for 7 to 14 days.	
Reporting group title	Cohort 1: Colistin
Reporting group description: Subjects received a 5 mg/kg IV loading dose (300 mg maximum) colistin (plus meropenem or tigecycline) followed by a 5 mg/kg/d maintenance dose divided into every 8 hours (q8h) or every 12 hours (q12h) for 7 to 14 days.	
Reporting group title	Cohort 2: Plazomicin-Based Therapy
Reporting group description: Subjects received 15 mg/kg as a 30 minute IV infusion once daily. Bloodstream infection (BSI), hospital acquired bacterial pneumonia (HABP) or ventilator associated bacterial pneumonia (VABP) subjects received plazomicin and any supplemental antibiotic therapy, according to Investigator's choice, for 7 to 14 days. Complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) subjects received plazomicin monotherapy only for 4 to 7 days with an option to switch to oral therapy on or after Day 5.	
Subject analysis set title	Plazomicin
Subject analysis set type	Sub-group analysis
Subject analysis set description: PK blood samples were collected on Days 1 and 4 (plus or minus 1 calendar day) from all plazomicin-treated patients for the determination of plazomicin plasma concentrations.	

### Primary: Percentage of Subjects With All Cause Mortality (ACM) at Day 28 or Significant Disease-Related Complication (SDRC) in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1

End point title	Percentage of Subjects With All Cause Mortality (ACM) at Day 28 or Significant Disease-Related Complication (SDRC) in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1 <sup>[1]</sup>
End point description: ACM at Day 28: confirmed date of death within 28 days of the first dose of study drug, irrespective of causality. SDRCs for all subjects: presence of 1 or more of the following complications within 7 days of randomisation: new or worsening acute respiratory distress syndrome (ARDS), new lung abscess, new empyema, new onset of septic shock, new Carbapenem Resistant Enterobacteriaceae (CRE) (HABP/VABP subjects only); persistent bacteremia on study Day $\geq 5$ (BSI subjects only). The mMITT population was a subset of the MITT population and included all subjects who received at least 1 dose of study drug and had a CRE pathogen. CRE= meropenem minimum inhibitory concentration (MIC) of $\geq 4$ gram per milliliter (g/mL) or meropenem MIC= 2 g/mL and disk diffusion results ( $\leq 19$ millimetre [mm]) indicating meropenem resistance, isolated from an acceptable study-qualifying baseline blood (BSI subjects) or lower respiratory tract (HABP/VABP subjects) specimen.	
End point type	Primary
End point timeframe: Up to Day 28 for ACM, up to 7 Days for SDRCs in all Subjects, on or after Day 5 for Bloodstream Infection Subjects Only.	

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 2 are not presented here as this Cohort was not part of the primary or key secondary endpoints per the protocol and statistical analysis plan.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: percentage of subjects				
number (not applicable)	23.5	50		

## Statistical analyses

Statistical analysis title	Colistin vs Plazomicin
Statistical analysis description: The 2-sided 90% confidence interval (CI) for the difference between groups in Cohort 1 (colistin minus plazomicin) is based on the unconditional exact method.	
Comparison groups	Cohort 1: Colistin v Cohort 1: Plazomicin
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
Method	1-sided Fisher's exact test
Parameter estimate	Difference Estimate
Point estimate	26.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.7
upper limit	51.2

## Secondary: Percentage of Subjects With All Cause Mortality (ACM) at Day 28 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1

End point title	Percentage of Subjects With All Cause Mortality (ACM) at Day 28 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1 <sup>[2]</sup>
-----------------	---

### End point description:

All cause mortality at Day 28: confirmed date of death within 28 days of the first dose of study drug, irrespective of causality. The mMITT population was a subset of MITT population and included all subjects who received at least 1 dose of study drug and had a CRE pathogen. CRE= meropenem MIC of  $\geq 4$  g/mL or meropenem MIC= 2 g/mL and disk diffusion results ( $\leq 19$  mm) indicating meropenem resistance, isolated from an acceptable study-qualifying baseline blood (BSI subjects) or lower respiratory tract (HABP/VABP subjects) specimen.

End point type	Secondary
----------------	-----------

### End point timeframe:

Up to Day 28

### Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 2 are not presented here as this Cohort was not part of the primary or key secondary endpoints per the protocol and statistical analysis plan.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: percentage of subjects				
number (not applicable)	11.8	40		

## Statistical analyses

Statistical analysis title	Colistin vs Plazomicin
Statistical analysis description:	
The 2-sided 90% confidence interval (CI) for the difference between groups in Cohort 1 (colistin minus plazomicin) is based on the unconditional exact method.	
Comparison groups	Cohort 1: Plazomicin v Cohort 1: Colistin
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
Method	1-sided Fisher's exact test
Parameter estimate	Difference Estimate
Point estimate	28.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	52.5

## Secondary: Percentage of Subjects with Adjudicated Clinical Cure at the Test of Cure (TOC) Visit in Subjects in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1

End point title	Percentage of Subjects with Adjudicated Clinical Cure at the Test of Cure (TOC) Visit in Subjects in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1 <sup>[3]</sup>
-----------------	---

### End point description:

Clinical response was assessed at EOT in all subjects and at TOC for subjects who were a clinical cure or had an indeterminate outcome at the most recent assessment visit. Assessment of clinical response at TOC was not needed for subjects who were a clinical failure at an earlier assessment visit. Clinical outcomes at both EOT and TOC were independently adjudicated by a committee external to the Sponsor who were blinded to treatment assignment. The assessment of clinical response was confounded by comorbidities and the occurrence of additional infections in this high-risk subject population. Thus, adjudicating clinical response of the baseline CRE infection was influenced by confounding signs and symptoms of unrelated infections or conditions. The difficulty assessing clinical responses supports greater reliance on the more objective mortality-based primary endpoint in these critically ill subjects, particularly in an ITT Population analysis.

End point type	Secondary
----------------	-----------

### End point timeframe:

Up to TOC (Day 23)

### Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 2 are not presented here as this Cohort was not part of the primary or key secondary endpoints per the protocol and statistical analysis plan.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: percentage of subjects				
number (not applicable)				
EOT Visit: Clinical Cure	64.7	45		
EOT Visit: Clinical Failure	35.3	55		
TOC Visit: Clinical Cure	35.3	35		
TOC Visit: Clinical Failure	58.8	65		
TOC Visit: Indeterminate Response	5.9	0		

## Statistical analyses

Statistical analysis title	Colistin vs Plazomicin
Statistical analysis description:	
The 2-sided 90% confidence interval (CI) for the difference in clinical cure percentage at the TOC visit between groups in Cohort 1 (colistin minus plazomicin) is based on the unconditional exact method.	
Comparison groups	Cohort 1: Plazomicin v Cohort 1: Colistin
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
Method	1-sided Fisher's exact test
Parameter estimate	Difference Estimate
Point estimate	-0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-26.9
upper limit	26.8

## Secondary: Time to Death Through Day 28 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1

End point title	Time to Death Through Day 28 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1 <sup>[4]</sup>
End point description:	
Time to death through Day 28 is defined as days from first dose of study drug to death from any cause on or before Day 28. Subjects who were alive at Day 28 were censored on Day 28. Any subject whose survival status was not known at Day 28 was censored on the last known date alive. The mMITT population included all subjects who received at least 1 dose of study drug and had a CRE pathogen. CRE= meropenem minimum inhibitory concentration (MIC) of $\geq 4$ gram per milliliter (g/mL) or meropenem MIC= 2 g/mL and disk diffusion results ( $\leq 19$ millimetre [mm]) indicating meropenem resistance, isolated from an acceptable study-qualifying baseline blood (BSI subjects) or lower respiratory tract (HABP/VABP subjects) specimen.	
End point type	Secondary
End point timeframe:	
Up to Day 28.	

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 2 are not presented here as this Cohort was not part of the primary or key secondary endpoints per the protocol and statistical analysis plan.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: Percentage of Subjects				
number (not applicable)				
Died by Day 28	11.8	40		
Censored at 28 days	88.2	60		
Censored at <28 days	0	0		

## Statistical analyses

Statistical analysis title	Colistin vs Plazomicin
Statistical analysis description: The 2-sided 90% confidence interval (CI) for the unadjusted hazard ratio between groups in Cohort 1 (colistin:plazomicin) is based on a Cox proportional hazards regression model.	
Comparison groups	Cohort 1: Plazomicin v Cohort 1: Colistin
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
Method	1-sided logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	3.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	14.61

## Secondary: Percentage of Subjects With All Cause Mortality (ACM) at Day 14 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1

End point title	Percentage of Subjects With All Cause Mortality (ACM) at Day 14 in the Microbiological Modified Intent to Treat (mMITT) Population in Cohort 1 <sup>[5]</sup>
End point description: ACM at Day 14 was defined as a confirmed date of death within 14 days of the first dose of study drug, irrespective of causality. The mMITT population was a subset of MITT population and included all subjects who received at least 1 dose of study drug and had a CRE pathogen. CRE= meropenem MIC of >=4 g/mL or meropenem MIC= 2 g/mL and disk diffusion results (<=19 mm) indicating meropenem resistance, isolated from an acceptable study-qualifying baseline blood (BSI subjects) or lower respiratory tract (HABP/VABP subjects) specimen.	
End point type	Secondary
End point timeframe: Day 14	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 2 are not presented here as this Cohort was not part of the primary or key secondary endpoints per the protocol and statistical analysis plan.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: percentage of subjects				
number (not applicable)	5.9	20		

## Statistical analyses

Statistical analysis title	Colistin vs Plazomicin
Statistical analysis description: The two-sided 90% confidence interval for the difference between groups in Cohort 1 (colistin minus plazomicin) is based on the unconditional exact method.	
Comparison groups	Cohort 1: Plazomicin v Cohort 1: Colistin
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
Method	1-sided Fisher's exact test
Parameter estimate	Difference estimate
Point estimate	14.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13
upper limit	40.3

## Secondary: Percentage of Subjects With Dose Adjustment due to Therapeutic Drug Management (TDM)

End point title	Percentage of Subjects With Dose Adjustment due to Therapeutic Drug Management (TDM) <sup>[6]</sup>
End point description: After the initial plazomicin dose, subsequent doses were adjusted, as directed, with the use of TDM on Day 1, 4, and 8 as needed. The safety population included all randomised subjects who received any amount of study drug.	
End point type	Secondary
End point timeframe: Up to Day 14.	

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for Cohort 1: Colistin are not presented here as TDM collection does not apply to and was not collected for subjects in the colistin arm, as only plazomicin levels were measured.

End point values	Cohort 1: Plazomicin	Cohort 2: Plazomicin- Based Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	30		
Units: Percentage of Subjects				
number (not applicable)	77.8	86.7		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)
-----------------	--

End point description:

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered to be drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and it does not imply any judgment about causality. Adverse events also include the exacerbation or worsening of a condition present at screening other than the index infection for which the subject was enrolled in the study. The safety population included all randomised subjects who received any amount of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Day 67.

End point values	Cohort 1: Plazomicin	Cohort 1: Colistin	Cohort 2: Plazomicin- Based Therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	21	30	
Units: Percentage of Subjects				
number (not applicable)	88.9	100	86.7	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Pharmacokinetics (PK): Area Under the Curve from 0 to 24 Hours (AUC 0–24h)

End point title	Plasma Pharmacokinetics (PK): Area Under the Curve from 0 to 24 Hours (AUC 0–24h)
-----------------	---

End point description:

PK blood samples were collected on Days 1 and 4 (plus or minus 1 calendar day) from all plazomicin-treated subjects for the determination of plazomicin plasma concentrations. PK population included all subjects who had received at least 1 dose of plazomicin and had at least 1 quantifiable plazomicin plasma concentration available for analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1 and 4

<b>End point values</b>	Plazomicin			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: mg * h/L				
geometric mean (geometric coefficient of variation)	235 (± 42)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Pharmacokinetics (PK): Maximum Observed Plasma Drug Concentration (Cmax)

End point title	Plasma Pharmacokinetics (PK): Maximum Observed Plasma Drug Concentration (Cmax)
-----------------	---

End point description:

PK blood samples were collected on Days 1 and 4 (plus or minus 1 calendar day) from all plazomicin-treated subjects for the determination of plazomicin plasma concentrations. PK population included all subjects who had received at least 1 dose of plazomicin and had at least 1 quantifiable plazomicin plasma concentration available for analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1 and 4

<b>End point values</b>	Plazomicin			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: mg/L				
geometric mean (geometric coefficient of variation)	37.1 (± 39.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Pharmacokinetics (PK): Minimum Observed Plasma Drug Concentration (Cmin)

End point title	Plasma Pharmacokinetics (PK): Minimum Observed Plasma Drug Concentration (Cmin)
-----------------	---



---

**End point description:**

PK blood samples were collected on Days 1 and 4 (plus or minus 1 calendar day) from all plazomicin-treated subjects for the determination of plazomicin plasma concentrations. PK population included all subjects who had received at least 1 dose of plazomicin and had at least 1 quantifiable plazomicin plasma concentration available for analysis.

---

End point type	Secondary
----------------	-----------

---

**End point timeframe:**

Days 1 and 4

---

End point values	Plazomicin			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: mg/L				
geometric mean (geometric coefficient of variation)	2.1 ( $\pm$ 99.4)			

---

**Statistical analyses**

No statistical analyses for this end point

---

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 67

Adverse event reporting additional description:

The safety population included all randomised subjects who received any amount of intravenous (IV) study drug. Because of the small sample size enrolled and the requirement to report AEs occurring in  $\geq 5\%$  of patients, all AEs are reported here, including those occurring in only a single patient.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

### Reporting groups

Reporting group title	Cohort 1: Plazomicin
-----------------------	----------------------

Reporting group description:

Subjects received 15 mg/kg plazomicin as a 30-minute infusion once daily.

Reporting group title	Cohort 1: Colistin
-----------------------	--------------------

Reporting group description:

Subjects received colistin as a 5-mg/kg IV loading dose (300 mg maximum) followed by a 5-mg/kg/d maintenance dose divided into every 8 hours (q8h) or every 12 hours (q12h).

Reporting group title	Cohort 2: Plazomicin-Based Therapy
-----------------------	------------------------------------

Reporting group description:

Subjects assigned to plazomicin received 15 mg/kg as a 30 minute IV infusion once daily. BSI, HABP or VABP subjects received Plazomicin and any supplemental antibiotic. cUTI or AP subjects received Plazomicin monotherapy only with an option to switch to oral therapy.

Serious adverse events	Cohort 1: Plazomicin	Cohort 1: Colistin	Cohort 2: Plazomicin-Based Therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 18 (50.00%)	17 / 21 (80.95%)	20 / 30 (66.67%)
number of deaths (all causes)	8	13	12
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Blood creatinine increased			

subjects affected / exposed	0 / 18 (0.00%)	2 / 21 (9.52%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pneumonitis chemical			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 18 (5.56%)	2 / 21 (9.52%)	4 / 30 (13.33%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 4
Cardio-respiratory arrest			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 18 (11.11%)	3 / 21 (14.29%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis infectious			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia necrotising			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 18 (0.00%)	3 / 21 (14.29%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Septic shock			
subjects affected / exposed	4 / 18 (22.22%)	5 / 21 (23.81%)	5 / 30 (16.67%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 5	0 / 4
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	4 / 30 (13.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperosmolar state			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Cohort 1: Plazomicin	Cohort 1: Colistin	Cohort 2: Plazomicin-Based Therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	20 / 21 (95.24%)	22 / 30 (73.33%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	3 / 30 (10.00%)
occurrences (all)	1	0	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 18 (0.00%)	2 / 21 (9.52%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Pleural effusion			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Pneumothorax			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 18 (0.00%)	2 / 21 (9.52%)	3 / 30 (10.00%)
occurrences (all)	0	2	3
Depression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Blood creatinine increased			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 21 (9.52%) 3	1 / 30 (3.33%) 1
Blood fibrinogen decreased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 21 (0.00%) 0	0 / 30 (0.00%) 0
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 21 (4.76%) 1	2 / 30 (6.67%) 2
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	1 / 21 (4.76%) 1	2 / 30 (6.67%) 2
Extrasystoles subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 21 (0.00%) 0	0 / 30 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 4	2 / 21 (9.52%) 2	1 / 30 (3.33%) 1
Leukocytosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 21 (0.00%) 0	0 / 30 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	2 / 21 (9.52%) 2	2 / 30 (6.67%) 2
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	0 / 21 (0.00%) 0	1 / 30 (3.33%) 1
Diarrhoea subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	2 / 21 (9.52%) 2	3 / 30 (10.00%) 3
Nausea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 21 (4.76%) 1	3 / 30 (10.00%) 3
Vomiting			



subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 21 (9.52%) 2	2 / 30 (6.67%) 2
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Penile ulceration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 18 (11.11%)	4 / 21 (19.05%)	5 / 30 (16.67%)
occurrences (all)	2	4	5
Haematuria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Fungal sepsis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Oral fungal infection			

subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 21 (9.52%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Sepsis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Skin infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Stoma site abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Systemic candida			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tinea cruris			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tracheobronchitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Hypernatraemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	2 / 30 (6.67%)
occurrences (all)	1	1	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 21 (9.52%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Hypocalcaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2

Hypokalaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	2 / 30 (6.67%)
occurrences (all)	1	1	2
Hypomagnesaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	2 / 30 (6.67%)
occurrences (all)	1	1	3
Hypophosphataemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	2 / 30 (6.67%)
occurrences (all)	0	1	2

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2015	<ol style="list-style-type: none"><li>1. Protocol amended to address enrollment changes<ol style="list-style-type: none"><li>a. A lower than expected incidence of the study-qualifying infections due to carbapenem resistant Enterobacteriaceae (CRE)</li><li>b. Challenges in meeting the eligibility criteria due to prolonged turnaround times in microbiology laboratories</li><li>c. Overly stringent inclusion criteria for the diagnosis of ventilator associated bacterial pneumonia (VABP)</li><li>d. Burdensome pharmacokinetic (PK) assessments</li><li>e. Requirement for adjunctive tigecycline to be used at doses lower than the institutional standard of care for serious infections due to CRE</li><li>f. Complex dose adjustments for plazomicin</li></ol></li><li>2. Primary endpoint was amended to include SDRCs that are more infection attributable than ACM</li></ol>
13 July 2015	<ol style="list-style-type: none"><li>1. Added a second nonrandomized cohort of subjects (Cohort 2) with serious infections that had a high likelihood of being due to CRE but who were excluded from enrollment in the randomized cohort</li></ol>

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Due to challenges with enrolling the study, it was stopped early and thus, it did not reach the originally planned sample size and was not adequately powered.

Notes: