# 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 205/28/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 |
| **Arm title** | Cohort 1: Plazomicin |

Arm description:

Subjects received 15 milligram per killogram (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.

| | |
|---|---|
| **Arm title** | 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 >=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.

| | |
|---|---|
| **Arm title** | 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 killogram (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<br>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<br>Units: years | | | |
| arithmetic mean | 64.94 | 63.29 | 62.8 |
| standard deviation | ± 13.94 | ± 18.25 | ± 18.15 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 11 | 7 |
| Male | 12 | 10 | 23 |

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

| | | | |
|---|---|---|---|
| Gender categorical<br>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 plazomcin-treated patients for the determination of plazomicin plasma concentrations.

| **Reporting group values** | Plazomicin | | |
|---|---|---|---|
| Number of subjects | 48 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 19 | | |
| From 65-84 years | 29 | | |
| 85 years and over | 0 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.6 | | |
| standard deviation | ± 16.57 | | |
| Gender categorical<br>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 killogram (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 plazomcin-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[1] |
|---|---|

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 ≥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 >=4 gram per milliliter (g/mL) or meropenem MIC= 2 g/mL and disk diffusion results (<=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[2] |
|---|---|
| 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 >=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: | |
| 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[3] |
|---|---|

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: percenatge 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[4] |
|---|---|
| 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 >=4 gram per milliliter (g/mL) or meropenem MIC= 2 g/mL and disk diffusion results (<=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[5] |
|---|---|

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)[6] |
|---|---|

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 plazomcin-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 * 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 plazomcin-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) | 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 plazomcin-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 (± 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 => 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 %

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 21 (9.52%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 | 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 | 1. Protocol amended to address enrollment changes<br>a. A lower than expected incidence of the study-qualifying infections due to carbapenem resistant Enterobacteriaceae (CRE)<br>b. Challenges in meeting the eligibility criteria due to prolonged turnaround times in microbiology laboratories<br>c. Overly stringent inclusion criteria for the diagnosis of ventilator associated bacterial pneumonia (VABP)<br>d. Burdensome pharmacokinetic (PK) assessments<br>e. Requirement for adjunctive tigecycline to be used at doses lower than the institutional standard of care for serious infections due to CRE<br>f. Complex dose adjustments for plazomicin<br>2. Primary endpoint was amended to include SDRCs that are more infection attributable than ACM |
| 13 July 2015 | 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 |

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: