



## Clinical trial results:

### A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2011-003895-35          |
| Trial protocol           | DE BE CZ GR ES BG IT LT |
| Global end of trial date | 07 April 2014           |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 February 2017 |
| First version publication date | 06 August 2015   |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | D4280C00001/5 |
|-----------------------|---------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AstraZeneca  |
| Sponsor organisation address | Alderley Park, Macclesfield, United Kingdom, SK10 4TG                              |
| Public contact               | Paul Newell, Medical Science Director, AstraZeneca,<br>paul.newell@astrazeneca.com |
| Scientific contact           | Paul Newell, Medical Science Director, AstraZeneca,<br>paul.newell@astrazeneca.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                       | 01 August 2014 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 07 April 2014  |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 07 April 2014  |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the noninferiority of CAZ AVI plus metronidazole compared to meropenem with respect to clinical cure at the TOC visit. For US FDA the primary objective was assessed in patients who have at least 1 identified pathogen (the microbiologically modified intent-to-treat (mMITT) analysis set). For the rest of world, the primary objective was assessed in patients in the modified-intent-to-treat (MITT) analysis set and in patients who are clinically evaluable (CE).

Protection of trial subjects:

The final study protocol, including the final version of the informed consent form and any other written information or materials provided to the patients was approved by an independent ethics committee (EC) and/or institutional review board (IRB). The investigator ensured the distribution of these documents to the applicable EC and to the study center personnel. This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1) Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy:

Patients in the CAZ-AVI treatment group also received Metronidazole. If Enterococcus species or MRSA was one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy was indicated, then open-label vancomycin, linezolid, or daptomycin may have been added to either of the study regimens according to the usual practice of the investigator.

Evidence for comparator:

Patients in the comparator treatment group received Meropenem. If Enterococcus species or MRSA was one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy was indicated, then open-label vancomycin, linezolid, or daptomycin may have been added to either of the study regimens according to the usual practice of the investigator.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 22 March 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Bulgaria: 66        |
| Country: Number of subjects enrolled | Croatia: 1          |
| Country: Number of subjects enrolled | Czech Republic: 243 |
| Country: Number of subjects enrolled | Hungary: 15         |
| Country: Number of subjects enrolled | Latvia: 2           |
| Country: Number of subjects enrolled | Lithuania: 7        |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 144           |
| Country: Number of subjects enrolled | Russian Federation: 49 |
| Country: Number of subjects enrolled | Turkey: 2              |
| Country: Number of subjects enrolled | Ukraine: 99            |
| Country: Number of subjects enrolled | Belgium: 5             |
| Country: Number of subjects enrolled | Canada: 1              |
| Country: Number of subjects enrolled | France: 16             |
| Country: Number of subjects enrolled | Germany: 2             |
| Country: Number of subjects enrolled | Italy: 1               |
| Country: Number of subjects enrolled | Netherlands: 3         |
| Country: Number of subjects enrolled | Spain: 30              |
| Country: Number of subjects enrolled | United States: 85      |
| Country: Number of subjects enrolled | Argentina: 11          |
| Country: Number of subjects enrolled | Brazil: 9              |
| Country: Number of subjects enrolled | Chile: 1               |
| Country: Number of subjects enrolled | India: 125             |
| Country: Number of subjects enrolled | Israel: 15             |
| Country: Number of subjects enrolled | Malaysia: 2            |
| Country: Number of subjects enrolled | Mexico: 20             |
| Country: Number of subjects enrolled | Peru: 36               |
| Country: Number of subjects enrolled | South Africa: 4        |
| Country: Number of subjects enrolled | Taiwan: 17             |
| Country: Number of subjects enrolled | Thailand: 21           |
| Country: Number of subjects enrolled | Greece: 34             |
| Worldwide total number of subjects   | 1066                   |
| EEA total number of subjects         | 569                    |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 821 |
| From 65 to 84 years                       | 227 |
| 85 years and over                         | 18  |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was enrolled on 22 March 2012 and the last patient's last visit was 07 April 2014. Patients were adults who were hospitalised with complicated intra-abdominal infection (cIAI) that required surgery and IV antibiotics.

### Pre-assignment

Screening details:

After obtaining written informed consent patients underwent a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy. eligible patients were randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall Study (overall period)                                |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | CAZ-AVI + Metronidazole |

Arm description:

CAZ (2000mg)/AVI (500mg): IV treatment

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Metronidazole         |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Metronidazole 500 mg/100 mL solution for infusion

|  |  |
|--|--|
| Investigational medicinal product name | CAZ-AVI  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

single vial filled with the sterile crystalline form of ceftazidime (2000 mg) and the sterile crystalline form of avibactam (500 mg)

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Meropenem |
|------------------|-----------|

Arm description:

1000 mg: IV treatment

|  |                                  |
|--|----------------------------------|
| Arm type                               | Active comparator                |
| Investigational medicinal product name | Meropenem                        |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

| <b>Number of subjects in period 1</b> | CAZ-AVI +<br>Metronidazole | Meropenem |
|---------------------------------------|----------------------------|-----------|
| Started                               | 532                        | 534       |
| Completed                             | 474                        | 494       |
| Not completed                         | 58                         | 40        |
| Consent withdrawn by subject          | 22                         | 17        |
| Adverse event, non-fatal              | 14                         | 7         |
| Not specified in study report         | 12                         | 6         |
| Condition improved/subject recovered  | 1                          | -         |
| Lack of efficacy                      | 7                          | 8         |
| Protocol deviation                    | 2                          | 2         |

## Baseline characteristics

### Reporting groups

|  |                         |
|--|-------------------------|
| Reporting group title  | CAZ-AVI + Metronidazole |
| Reporting group description:<br>CAZ (2000mg)/AVI (500mg): IV treatment |                         |
| Reporting group title  | Meropenem               |
| Reporting group description:<br>1000 mg: IV treatment                  |                         |

| Reporting group values                                | CAZ-AVI +<br>Metronidazole | Meropenem | Total |
|---|----------------------------|-----------|-------|
| Number of subjects                                    | 532                        | 534       | 1066  |
| Age categorical<br>Units: Subjects                    |                            |           |       |
| In utero  | 0                          | 0         | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                          | 0         | 0     |
| Newborns (0-27 days)                                  | 0                          | 0         | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                          | 0         | 0     |
| Children (2-11 years)                                 | 0                          | 0         | 0     |
| Adolescents (12-17 years)                             | 0                          | 0         | 0     |
| Adults (18-64 years)                                  | 411                        | 410       | 821   |
| From 65-84 years                                      | 115                        | 112       | 227   |
| 85 years and over                                     | 6                          | 12        | 18    |
| Age Continuous  <br>Units: Years                      |                            |           |       |
| arithmetic mean                                       | 49.8                       | 50.3      |       |
| standard deviation                                    | ± 17.48                    | ± 18.29   | -     |
| Gender, Male/Female<br>Units: Participants            |                            |           |       |
| Female  | 204                        | 200       | 404   |
| Male  | 328                        | 334       | 662   |

## End points

### End points reporting groups

|  |                         |
|--|-------------------------|
| Reporting group title  | CAZ-AVI + Metronidazole |
| Reporting group description:<br>CAZ (2000mg)/AVI (500mg): IV treatment |                         |
| Reporting group title  | Meropenem               |
| Reporting group description:<br>1000 mg: IV treatment                  |                         |

### Primary: Clinical response at the Test of Cure (TOC) visit in the microbiologically Modified Intent-To-Treat (mMITT) analysis set (primary outcome for FDA).

|  |   |
|--|---|
| End point title  | Clinical response at the Test of Cure (TOC) visit in the microbiologically Modified Intent-To-Treat (mMITT) analysis set (primary outcome for FDA). |
| End point description:<br>The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention is necessary. |   |
| End point type   | Primary   |
| End point timeframe:<br>TOC: 28 to 35 days after start of study drug   |   |

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 413                     | 410             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 337                     | 349             |  |  |
| Clinical failure            | 37                      | 30              |  |  |
| Indeterminate               | 39                      | 31              |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title  | Non-inferiority                     |
| Statistical analysis description:<br>The primary objective of this study (FDA agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the mMITT in adult subjects with cIAI. |                                     |
| Comparison groups   | CAZ-AVI + Metronidazole v Meropenem |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 823                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Parameter estimate                      | Risk difference (RD)           |
| Point estimate                          | -3.5                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -8.64                          |
| upper limit                             | 1.58                           |

Notes:

[1] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority margin of -12.5%

### **Primary: Clinical response at the TOC visit in the Modified Intent-To-Treat analysis set (co-primary outcome for Rest of World [ROW]).**

|                 |   |
|-----------------|---|
| End point title | Clinical response at the TOC visit in the Modified Intent-To-Treat analysis set (co-primary outcome for Rest of World [ROW]). |
|-----------------|---|

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

TOC: 28 to 35 days after start of study drug

| <b>End point values</b>     | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 520                     | 523             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 429                     | 444             |  |  |
| Clinical failure            | 47                      | 39              |  |  |
| Indeterminate               | 44                      | 40              |  |  |

### **Statistical analyses**

|                                   |                 |
|-----------------------------------|-----------------|
| <b>Statistical analysis title</b> | Non-inferiority |
|-----------------------------------|-----------------|

Statistical analysis description:

The co-primary objective of this study (ROW agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the MITT in adult subjects with cIAI.

|                   |                                     |
|-------------------|-------------------------------------|
| Comparison groups | CAZ-AVI + Metronidazole v Meropenem |
|-------------------|-------------------------------------|



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 1043                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| Parameter estimate                      | Risk difference (RD)           |
| Point estimate                          | -2.4                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -6.9                           |
| upper limit                             | 2.1                            |

Notes:

[2] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority margin of -12.5%

### **Primary: Clinical response at the TOC visit in the Clinically Evaluable (CE) analysis set (co-primary outcome for Rest of World [ROW]).**

|                 |  |
|-----------------|--|
| End point title | Clinical response at the TOC visit in the Clinically Evaluable (CE) analysis set (co-primary outcome for Rest of World [ROW]). |
|-----------------|--|

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

TOC: 28 to 35 days after start of study drug

| <b>End point values</b>     | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 410                     | 416             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 376                     | 385             |  |  |
| Clinical failure            | 34                      | 31              |  |  |

### **Statistical analyses**

|                                   |                 |
|-----------------------------------|-----------------|
| <b>Statistical analysis title</b> | Non-inferiority |
|-----------------------------------|-----------------|

Statistical analysis description:

The co-primary objective of this study (ROW agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the CE in adult subjects with cIAI.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | CAZ-AVI + Metronidazole v Meropenem |
| Number of subjects included in analysis | 826                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | non-inferiority <sup>[3]</sup>      |
| Parameter estimate                      | Risk difference (RD)                |
| Point estimate                          | -0.8                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4.61   |
| upper limit         | 2.89    |

Notes:

[3] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority margin of -12.5%

### Secondary: Clinical cure at TOC in the microbiologically evaluable analysis set

|                 |  |
|-----------------|--|
| End point title | Clinical cure at TOC in the microbiologically evaluable analysis set |
|-----------------|--|

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

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

End point timeframe:

TOC: 28 to 35 days after start of study drug

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 265                     | 287             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 244                     | 272             |  |  |
| Clinical failure            | 21                      | 15              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical cure at TOC in the extended microbiologically evaluable analysis set

|                 |   |
|-----------------|---|
| End point title | Clinical cure at TOC in the extended microbiologically evaluable analysis set |
|-----------------|---|

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

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

End point timeframe:

TOC: 28 to 35 days after start of study drug

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 270                     | 294             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 248                     | 278             |  |  |
| Clinical failure            | 22                      | 16              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at EOT visit

|                        |   |
|------------------------|---|
| End point title        | Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at EOT visit   |
| End point description: | Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary. |
| End point type         | Secondary   |
| End point timeframe:   | EOT: within 24 hours after last dose of study drug.   |

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 413                     | 410             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical cure               | 361                     | 379             |  |  |
| Clinical failure            | 30                      | 19              |  |  |
| Indeterminate               | 22                      | 12              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Per-patient microbiological response in the microbiologically Modified Intent- To-Treat analysis set at TOC visit

|                        |  |
|------------------------|--|
| End point title        | Per-patient microbiological response in the microbiologically Modified Intent- To-Treat analysis set at TOC visit  |
| End point description: | Microbiological responses as per the protocol criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cases where the clinical response was changed to indeterminate due to an SRP assessment of inadequate source control (ie, |

circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

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

End point timeframe:

TOC: 28 to 35 days after start of study drug.

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 413                     | 410             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Favourable response         | 337                     | 349             |  |  |
| Unfavourable response       | 37                      | 31              |  |  |
| Indeterminate               | 39                      | 30              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Favorable per-pathogen microbiological response for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

|                 |  |
|-----------------|--|
| End point title | Favorable per-pathogen microbiological response for patients infected with ceftazidime-resistant pathogens in mMITT analysis set |
|-----------------|--|

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favourable microbiological response includes: Eradication Absence of causative pathogen from specimens at the site of infection. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.

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

End point timeframe:

TOC: 28 to 35 days after start of study drug

| End point values                      | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|---------------------------------------|-------------------------|-----------------|--|--|
| Subject group type                    | Reporting group         | Reporting group |  |  |
| Number of subjects analysed           | 48                      | 64              |  |  |
| Units: Number of favourable responses |                         |                 |  |  |
| Citrobacter freundii complex: n       | 1                       | 2               |  |  |
| Citrobacter freundii complex: cure    | 1                       | 2               |  |  |
| Enterobacter aerogenes: n             | 0                       | 1               |  |  |
| Enterobacter aerogenes: cure          | 0                       | 1               |  |  |
| Enterobacter cloacae: n               | 3                       | 7               |  |  |
| Enterobacter cloacae: cure            | 2                       | 7               |  |  |
| Escherichia coli: n                   | 24                      | 37              |  |  |
| Escherichia coli: cure                | 19                      | 31              |  |  |

|                              |    |    |  |  |
|------------------------------|----|----|--|--|
| Klebsiella pneumoniae: n     | 13 | 13 |  |  |
| Klebsiella pneumoniae: cure  | 10 | 9  |  |  |
| Morganella morganii: n       | 2  | 1  |  |  |
| Morganella morganii: cure    | 1  | 1  |  |  |
| Proteus mirabilis: n         | 2  | 3  |  |  |
| Proteus mirabilis: cure      | 2  | 3  |  |  |
| Serratia marcescens: n       | 1  | 0  |  |  |
| Serratia marcescens: cure    | 1  | 0  |  |  |
| Alcaligenes faecalis: n      | 1  | 2  |  |  |
| Alcaligenes faecalis: cure   | 1  | 2  |  |  |
| Comamonas testosteroni: n    | 1  | 0  |  |  |
| Comamonas testosteroni: cure | 1  | 0  |  |  |
| Pseudomonas aeruginosa: n    | 2  | 4  |  |  |
| Pseudomonas aeruginosa: cure | 2  | 4  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: The time to first defervescence in the clinically evaluable analysis set for patients who have fever at study entry

|                 |   |
|-----------------|---|
| End point title | The time to first defervescence in the clinically evaluable analysis set for patients who have fever at study entry |
|-----------------|---|

End point description:

Time to first defervescence was calculated for patients with a fever ( $>38^{\circ}\text{C}$ ) at baseline. Defervescence ( $\leq 37.8^{\circ}\text{C}$ ) was defined as the absence of fever based on the highest temperature recorded on each study day. Time to first defervescence while on IV study therapy in the CE analysis set at TOC for patients who had fever at study entry is defined as time (in days) from the first dose of IV study therapy to first absence of fever.

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

End point timeframe:

Test of Cure: 1 to 14 days after start of study drug

| End point values                     | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|--------------------------------------|-------------------------|-----------------|--|--|
| Subject group type                   | Reporting group         | Reporting group |  |  |
| Number of subjects analysed          | 84                      | 78              |  |  |
| Units: Number of patients            |                         |                 |  |  |
| Afebrile at time of last observation | 84                      | 72              |  |  |
| Censored at time of last observation | 0                       | 6               |  |  |

## Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | Time to first defervescence         |
| Comparison groups          | CAZ-AVI + Metronidazole v Meropenem |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 162           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | other         |
| P-value                                 | < 0.004       |
| Method                                  | Logrank       |

### Secondary: Plasma concentrations for ceftazidime and avibactam

|                 |  |
|-----------------|--|
| End point title | Plasma concentrations for ceftazidime and avibactam <sup>[4]</sup> |
|-----------------|--|

End point description:

Blood samples were taken from all patients on Day 3 for the pharmacokinetic evaluation of ceftazidime and avibactam plasma concentrations

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

End point timeframe:

Anytime within 15 minutes prior to or after stopping study drug, anytime between 30 and 90 minutes after stopping study drug, anytime between 300 minutes and 360 minutes after stopping study drug

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: Data not available.

| End point values                             | CAZ-AVI + Metronidazole |  |  |  |
|--|-------------------------|--|--|--|
| Subject group type                           | Reporting group         |  |  |  |
| Number of subjects analysed                  | 499                     |  |  |  |
| Units: Geometric means for CAZ and AVI concs |                         |  |  |  |
| geometric mean (full range (min-max))        |                         |  |  |  |
| Ceftazidime: 30 mins before or after         | 50823 (171 to 3110000)  |  |  |  |
| Ceftazidime: 30-90 mins after                | 40053.1 (155 to 235000) |  |  |  |
| Ceftazidime: 300-360 mins after              | 10967.6 (159 to 151000) |  |  |  |
| Avibactam: 30 mins before or after           | 9229.4 (13 to 693000)   |  |  |  |
| Avibactam: 30-90 mins after                  | 7163.9 (15 to 46800)    |  |  |  |
| Avibactam: 300-360 mins after                | 1690.7 (14 to 30800)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical response by pathogen at TOC for patients infected with ceftazidime-resistant pathogens in microbiological modified intent to treat analysis set

|                 |  |
|-----------------|--|
| End point title | Clinical response by pathogen at TOC for patients infected with ceftazidime-resistant pathogens in microbiological modified intent to treat analysis set |
|-----------------|--|

End point description:

Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

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

End point timeframe:

Test of Cure: 28 to 35 days after start of study drug

| End point values                    | CAZ-AVI +<br>Metronidazole | Meropenem       |  |  |
|-------------------------------------|----------------------------|-----------------|--|--|
| Subject group type                  | Reporting group            | Reporting group |  |  |
| Number of subjects analysed         | 47                         | 64              |  |  |
| Units: Number of clinical cures     |                            |                 |  |  |
| All : n                             | 47                         | 64              |  |  |
| All : cure                          | 39                         | 55              |  |  |
| Citrobacter freundii complex : n    | 1                          | 2               |  |  |
| Citrobacter freundii complex : cure | 1                          | 2               |  |  |
| Enterobacter aerogenes : n          | 0                          | 1               |  |  |
| Enterobacter aerogenes: cure        | 0                          | 1               |  |  |
| Enterobacter cloacae : n            | 3                          | 7               |  |  |
| Enterobacter cloacae : cure         | 2                          | 7               |  |  |
| Escherichia coli : n                | 24                         | 37              |  |  |
| Escherichia coli : cure             | 19                         | 31              |  |  |
| Klebsiella pneumoniae : n           | 13                         | 13              |  |  |
| Klebsiella pneumoniae : cure        | 10                         | 9               |  |  |
| Morganella morganii : n             | 2                          | 1               |  |  |
| Morganella morganii : cure          | 1                          | 1               |  |  |
| Proteus mirabilis : n               | 2                          | 3               |  |  |
| Proteus mirabilis : cure            | 2                          | 3               |  |  |
| Serratia marcescens : n             | 1                          | 0               |  |  |
| Serratia marcescens : cure          | 1                          | 0               |  |  |
| Alcaligenes faecalis : n            | 1                          | 2               |  |  |
| Alcaligenes faecalis : cure         | 1                          | 2               |  |  |
| Comamonas testosteroni : n          | 1                          | 0               |  |  |
| Comamonas testosteroni : cure       | 1                          | 0               |  |  |
| Pseudomonas aeruginosa : n          | 2                          | 4               |  |  |
| Pseudomonas aeruginosa : cure       | 2                          | 4               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Per-patient microbiological response at TOC for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

|                 |  |
|-----------------|--|
| End point title | Per-patient microbiological response at TOC for patients infected with ceftazidime-resistant pathogens in mMITT analysis set |
|-----------------|--|

End point description:

Microbiological responses other than "indeterminate" were classified as "favorable" or "unfavorable."

Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cases where the clinical response was changed to indeterminate due to an SRP assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                  |           |
| Test of Cure: 28 to 35 days after start of study drug |           |

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 48                      | 64              |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Favourable                  | 39                      | 55              |  |  |
| Unfavourable                | 7                       | 1               |  |  |
| indeterminate               | 2                       | 8               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at LFU visit

|   |   |
|---|---|
| End point title   | Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at LFU visit |
| End point description:  |   |
| Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| LFU: 42 to 49 days after start of study drug  |   |

| End point values            | CAZ-AVI + Metronidazole | Meropenem       |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 413                     | 410             |  |  |
| Units: Number of patients   |                         |                 |  |  |
| Clinical Cure               | 340                     | 347             |  |  |
| Clinical Failure            | 38                      | 31              |  |  |
| Indeterminate               | 35                      | 32              |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Favourable per-pathogen microbiological response at TOC

|                 |   |
|-----------------|---|
| End point title | Favourable per-pathogen microbiological response at TOC |
|-----------------|---|

End point description:

The number of patients meeting favourable microbiological response (eradication or presumed eradication). Pathogens identified in 30 or more patients at baseline are shown here.

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

End point timeframe:

TOC: 28 to 35 days after start of study drug

| End point values                    | CAZ-AVI +<br>Metronidazole | Meropenem       |  |  |
|-------------------------------------|----------------------------|-----------------|--|--|
| Subject group type                  | Reporting group            | Reporting group |  |  |
| Number of subjects analysed         | 413                        | 410             |  |  |
| Units: Number of patients           |                            |                 |  |  |
| Escherichia coli: n                 | 271                        | 285             |  |  |
| Escherichia coli: cure              | 218                        | 249             |  |  |
| Streptococcus anginosus group: n    | 72                         | 61              |  |  |
| Streptococcus anginosus group: cure | 59                         | 50              |  |  |
| Klebsiella pneumoniae: n            | 51                         | 49              |  |  |
| Klebsiella pneumoniae: cure         | 40                         | 37              |  |  |
| Bacteroides fragilis: n             | 52                         | 47              |  |  |
| Bacteroides fragilis: cure          | 45                         | 38              |  |  |
| Pseudomonas aeruginosa: n           | 35                         | 36              |  |  |
| Pseudomonas aeruginosa: cure        | 30                         | 34              |  |  |
| Enterococcus faecalis: n            | 31                         | 28              |  |  |
| Enterococcus faecalis: cure         | 22                         | 23              |  |  |
| Bacteroides thetaiotaomicron: n     | 22                         | 25              |  |  |
| Bacteroides thetaiotaomicron: cure  | 18                         | 21              |  |  |
| Bacteroides ovatus: n               | 22                         | 20              |  |  |
| Bacteroides ovatus: cure            | 17                         | 17              |  |  |
| Enterococcus faecium: n             | 16                         | 22              |  |  |
| Enterococcus faecium: cure          | 13                         | 18              |  |  |
| Klebsiella oxytoca: n               | 18                         | 15              |  |  |
| Klebsiella oxytoca: cure            | 14                         | 12              |  |  |
| Enterobacter cloacae: n             | 13                         | 19              |  |  |
| Enterobacter cloacae: cure          | 11                         | 16              |  |  |
| Staphylococcus aureus: n            | 18                         | 14              |  |  |
| Staphylococcus aureus: cure         | 17                         | 14              |  |  |
| Citrobacter freundii complex: n     | 18                         | 12              |  |  |
| Citrobacter freundii complex: cure  | 14                         | 9               |  |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from screening/consent visit until late follow-up visit (Day -1/0 to Day 42). AE were summarised by number of patients. Number of occurrences were not summarised therefore number of patients are shown below.

Adverse event reporting additional description:

Number of occurrences were not reported in the CSR therefore number of patients shown here. Total number of patients with any AE are 233 vs 218. SAEs reported by  $\geq 2$  patients in either group, or any SAE with outcome of death, are reported here (total patients with SAE 42 vs 40).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 16.1   |

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Meropenem |
|-----------------------|-----------|

Reporting group description:

1000 mg: IV treatment

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | CAZ-AVI + Metronidazole |
|-----------------------|-------------------------|

Reporting group description:

CAZ (2000mg)/AVI (500mg): IV treatment.

| Serious adverse events                            | Meropenem        | CAZ-AVI + Metronidazole |  |
|---|------------------|-------------------------|--|
| Total subjects affected by serious adverse events |                  |                         |  |
| subjects affected / exposed                       | 18 / 529 (3.40%) | 26 / 529 (4.91%)        |  |
| number of deaths (all causes)                     | 5                | 8                       |  |
| number of deaths resulting from adverse events    | 0                | 0                       |  |
| Investigations                                    |                  |                         |  |
| Transaminases increased                           |                  |                         |  |
| subjects affected / exposed                       | 2 / 529 (0.38%)  | 0 / 529 (0.00%)         |  |
| occurrences causally related to treatment / all   | 1 / 2            | 0 / 0                   |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                   |  |
| Injury, poisoning and procedural complications    |                  |                         |  |
| Gastrointestinal stoma necrosis                   |                  |                         |  |
| subjects affected / exposed                       | 0 / 529 (0.00%)  | 2 / 529 (0.38%)         |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 2                   |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                   |  |
| Vascular disorders                                |                  |                         |  |
| Shock   |                  |                         |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 529 (0.00%) | 1 / 529 (0.19%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Cardiac disorders                                    |                 |                 |  |
| Myocardial infarct                                   |                 |                 |  |
| subjects affected / exposed                          | 2 / 529 (0.38%) | 1 / 529 (0.19%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |
| Cardiac failure                                      |                 |                 |  |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 2 / 529 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |
| Acute myocardial infarction                          |                 |                 |  |
| alternative dictionary used: MedDRA 16.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 1 / 529 (0.19%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Cardio-respiratory arrest                            |                 |                 |  |
| alternative dictionary used: MedDRA 16.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 0 / 529 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Blood and lymphatic system disorders                 |                 |                 |  |
| Disseminated intravascular coagulation               |                 |                 |  |
| subjects affected / exposed                          | 0 / 529 (0.00%) | 1 / 529 (0.19%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| General disorders and administration site conditions |                 |                 |  |
| Sudden death   |                 |                 |  |
| alternative dictionary used: MedDRA 16.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 529 (0.19%) | 1 / 529 (0.19%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 2 / 529 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 529 (0.57%) | 3 / 529 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 529 (0.19%) | 3 / 529 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 5 / 529 (0.95%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 529 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Candida sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 529 (0.00%) | 2 / 529 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 529 (0.38%) | 2 / 529 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hypoglycaemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 529 (0.38%) | 0 / 529 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Meropenem          | CAZ-AVI + Metronidazole |  |
|---|--------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events |                    |                         |  |
| subjects affected / exposed                           | 207 / 529 (39.13%) | 239 / 529 (45.18%)      |  |
| Vascular disorders                                    |                    |                         |  |
| Hypertension  |                    |                         |  |
| subjects affected / exposed                           | 24 / 529 (4.54%)   | 15 / 529 (2.84%)        |  |
| occurrences (all)                                     | 24                 | 15                      |  |
| Hypotension   |                    |                         |  |
| subjects affected / exposed                           | 12 / 529 (2.27%)   | 12 / 529 (2.27%)        |  |
| occurrences (all)                                     | 12                 | 12                      |  |
| Phlebitis   |                    |                         |  |
| subjects affected / exposed                           | 11 / 529 (2.08%)   | 10 / 529 (1.89%)        |  |
| occurrences (all)                                     | 11                 | 10                      |  |
| Nervous system disorders                              |                    |                         |  |
| Headache  |                    |                         |  |
| subjects affected / exposed                           | 9 / 529 (1.70%)    | 15 / 529 (2.84%)        |  |
| occurrences (all)                                     | 9                  | 15                      |  |
| General disorders and administration site conditions  |                    |                         |  |
| Pyrexia   |                    |                         |  |
| subjects affected / exposed                           | 24 / 529 (4.54%)   | 24 / 529 (4.54%)        |  |
| occurrences (all)                                     | 24                 | 24                      |  |
| Asthenia  |                    |                         |  |
| subjects affected / exposed                           | 12 / 529 (2.27%)   | 10 / 529 (1.89%)        |  |
| occurrences (all)                                     | 12                 | 10                      |  |
| Blood and lymphatic system disorders                  |                    |                         |  |
| Anaemia   |                    |                         |  |
| subjects affected / exposed                           | 9 / 529 (1.70%)    | 11 / 529 (2.08%)        |  |
| occurrences (all)                                     | 9                  | 11                      |  |
| Gastrointestinal disorders                            |                    |                         |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 17 / 529 (3.21%) | 40 / 529 (7.56%) |  |
| occurrences (all)                               | 17               | 40               |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                     | 24 / 529 (4.54%) | 36 / 529 (6.81%) |  |
| occurrences (all)                               | 24               | 36               |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 20 / 529 (3.78%) | 8 / 529 (1.51%)  |  |
| occurrences (all)                               | 20               | 8                |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 10 / 529 (1.89%) | 24 / 529 (4.54%) |  |
| occurrences (all)                               | 10               | 24               |  |
| Abdominal distensio                             |                  |                  |  |
| alternative dictionary used:<br>MedDRA 16.1     |                  |                  |  |
| subjects affected / exposed                     | 11 / 529 (2.08%) | 10 / 529 (1.89%) |  |
| occurrences (all)                               | 11               | 10               |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Cough   |                  |                  |  |
| subjects affected / exposed                     | 13 / 529 (2.46%) | 11 / 529 (2.08%) |  |
| occurrences (all)                               | 13               | 11               |  |
| Infections and infestations                     |                  |                  |  |
| Wound infection                                 |                  |                  |  |
| subjects affected / exposed                     | 11 / 529 (2.08%) | 13 / 529 (2.46%) |  |
| occurrences (all)                               | 11               | 13               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 31 October 2011 | Revised study plan to specify that additional ECGs are required in the event of a significant increase in QTcF (increase from baseline of $\geq 30$ msec or QTcF $> 460$ msec)  |
| 31 October 2011 | Revised concomitant and poststudy treatments to provide additional information on the potential interactions between meropenem and/or metronidazole and oral anticoagulants. Added prothrombin time test to coagulation monitoring tests in order to calculate the international normalized ratio |
| 16 July 2012    | Removal of genetic and biomarker sampling from study design   |
| 16 July 2012    | Revised to add the extended ME analysis set   |
| 16 July 2012    | Revision of inclusion criteria with respect to female contraception   |
| 16 July 2012    | Amended to allow enrollment of patients with open skin incisions (with fascial closure) for purposes of wound management, to clarify the timing of surgical wound examinations, and permit the use of negative pressure wound therapy.  |
| 16 July 2012    | Amended to revise the volume of blood drawn from each patient for PK and blood culture sampling and remove the pharmacogenetic and biomarker blood samples  |
| 31 July 2012    | Revised to allow the use of topical antibacterials and antifungals on sites other than the surgical site  |
| 31 July 2012    | Revised to clarify the collection of blood for Coombs test and culture  |
| 31 July 2012    | Revised to clarify follow-up procedures for patients who discontinued the study, or were enrolled in error/subsequently failed to meet entry criteria   |
| 29 July 2013    | Revised to combine the 2 identical protocols, D4280C00001 and D4280C00005, into a single study database for all analyses  |
| 29 July 2013    | Revised to clarify the structure and timing of visits and assessments   |
| 29 July 2013    | Revised inclusion criteria for female contraception and pregnancy   |
| 29 July 2013    | Amended to clarify that the IVRS system will be used to assign and enrollment code to the patients after consenting, but before eligibility is confirmed.   |
| 29 July 2013    | Amended to clarify that the initial dosing must be based on the estimated CrCl value at baseline, whereas, dose changes due to fluctuations in CrCl values may be made at the investigator's discretion   |
| 29 July 2013    | Amended to clarify that the use of concomitant antibiotics should not be withheld if the patient requires additional antibiotic therapy as a safety measure   |
| 29 July 2013    | Revision of the number of patients with perforated appendix and/or appendiceal abscess is increased to 40% of the study population  |



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Notes:

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### **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.

|  |
|--|
| This summary describes data collected from two identical CSPs (D4280C00005 and D4280C00005). With agreement from the EMA and the FDA the data have been combined into a single study database. |
|--|

Notes: