



## Clinical trial results:

### A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Intra-Abdominal Infection [cIAI]

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2011-005686-20             |
| Trial protocol           | DE ES PT GR LT LV EE BG PL |
| Global end of trial date | 11 August 2014             |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v2 (current)   |
| This version publication date  | 28 July 2019   |
| First version publication date | 01 August 2015 |
| Version creation reason        |                |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 7655-004 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01506271 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.  |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.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                       | 11 August 2014 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 11 August 2014 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 11 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy, safety and tolerability of adding 125 mg or 250 mg doses of MK-7655 (Relebactam) to imipenem/cilastatin in adults 18 years or older with complicated intra-abdominal infection (cIAI). The primary hypothesis is that the relebactam + imipenem/cilastatin treatment regimen is non-inferior to treatment with imipenem/cilastatin alone with respect to the proportion of participants with a favorable clinical response at completion of intravenous (IV) study therapy.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 31 May 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 | Argentina: 3           |
| Country: Number of subjects enrolled | Poland: 12             |
| Country: Number of subjects enrolled | Portugal: 10           |
| Country: Number of subjects enrolled | Bulgaria: 2            |
| Country: Number of subjects enrolled | Estonia: 14            |
| Country: Number of subjects enrolled | Germany: 9             |
| Country: Number of subjects enrolled | Greece: 6              |
| Country: Number of subjects enrolled | Latvia: 27             |
| Country: Number of subjects enrolled | Lithuania: 21          |
| Country: Number of subjects enrolled | Brazil: 3              |
| Country: Number of subjects enrolled | Colombia: 1            |
| Country: Number of subjects enrolled | Mexico: 6              |
| Country: Number of subjects enrolled | Peru: 7                |
| Country: Number of subjects enrolled | Romania: 62            |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | South Africa: 12       |
| Country: Number of subjects enrolled | Taiwan: 10             |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Turkey: 8         |
| Country: Number of subjects enrolled | Ukraine: 96       |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects   | 351               |
| EEA total number of subjects         | 163               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 271 |
| From 65 to 84 years                       | 77  |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Adult males or females 18 years old or older, with cIAI requiring treatment with IV antibiotic therapy were enrolled in this trial.

### Period 1

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

### Arms

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | Relebactam 250 mg + IPM/CIL |

Arm description:

Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Relebactam                                 |
| Investigational medicinal product code |  |
| Other name                             | MK-7655                                    |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Relebactam 250 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

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

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Relebactam 125 mg + IPM/CIL |
|------------------|-----------------------------|

Arm description:

Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Imipenem/Cilastatin                        |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|  |  |
|--|--|
| Investigational medicinal product name | Relebactam                                 |
| Investigational medicinal product code |  |
| Other name                             | MK-7655                                    |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Relebactam 125 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo + IPM/CIL |
|------------------|-------------------|

Arm description:

Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|  |  |
|--|--|
| Arm type                               | Placebo                                    |
| Investigational medicinal product name | Imipenem/Cilastatin                        |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Placebo for relebactam          |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Normal saline (0.9%) was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

| <b>Number of subjects in period 1</b> | Relebactam 250 mg<br>+ IPM/CIL | Relebactam 125 mg<br>+ IPM/CIL | Placebo + IPM/CIL |
|---------------------------------------|--------------------------------|--------------------------------|-------------------|
| Started                               | 118                            | 116                            | 117               |
| Treated                               | 117                            | 116                            | 114               |
| Completed                             | 114                            | 109                            | 114               |
| Not completed                         | 4                              | 7                              | 3                 |
| Adverse event, serious fatal          | -                              | 1                              | -                 |
| Consent withdrawn by subject          | -                              | 1                              | 1                 |
| Adverse event, non-fatal              | -                              | 2                              | -                 |
| Insufficient supply of study drug     | 1                              | -                              | -                 |
| Lost to follow-up                     | -                              | 1                              | 2                 |
| Progressive disease                   | -                              | 1                              | -                 |
| Protocol deviation                    | 3                              | 1                              | -                 |



## Baseline characteristics

### Reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title   | Relebactam 250 mg + IPM/CIL |
| Reporting group description:<br>Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours. |                             |
| Reporting group title   | Relebactam 125 mg + IPM/CIL |
| Reporting group description:<br>Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.                       |                             |
| Reporting group title   | Placebo + IPM/CIL           |
| Reporting group description:<br>Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.                  |                             |

| Reporting group values             | Relebactam 250 mg + IPM/CIL | Relebactam 125 mg + IPM/CIL | Placebo + IPM/CIL |
|------------------------------------|-----------------------------|-----------------------------|-------------------|
| Number of subjects                 | 118                         | 116                         | 117               |
| Age categorical<br>Units: Subjects |                             |                             |                   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 48.3<br>± 18.9 | 49.8<br>± 17.4 | 49.1<br>± 17.8 |
| Gender categorical<br>Units: Subjects                                   |                |                |                |
| Female  | 44             | 54             | 51             |
| Male  | 74             | 62             | 66             |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 351   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender categorical<br>Units: Subjects                                   |     |  |  |
| Female  | 149 |  |  |
| Male  | 202 |  |  |

## End points

### End points reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title   | Relebactam 250 mg + IPM/CIL |
| Reporting group description:<br>Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours. |                             |
| Reporting group title   | Relebactam 125 mg + IPM/CIL |
| Reporting group description:<br>Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.                       |                             |
| Reporting group title   | Placebo + IPM/CIL           |
| Reporting group description:<br>Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.                  |                             |

### Primary: Percentage of participants with a favorable clinical response at completion of IV study therapy

|   |   |
|---|---|
| End point title   | Percentage of participants with a favorable clinical response at completion of IV study therapy |
| End point description:<br>A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The microbiologically evaluable (ME) population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received $\geq 96$ hours of IV study therapy. |   |
| End point type  | Primary   |
| End point timeframe:<br>4 to 14 days post initiation of IV study therapy (up to post-randomization day 14)  |   |

| End point values                  | Relebactam 250 mg + IPM/CIL | Relebactam 125 mg + IPM/CIL | Placebo + IPM/CIL   |  |
|-----------------------------------|-----------------------------|-----------------------------|---------------------|--|
| Subject group type                | Reporting group             | Reporting group             | Reporting group     |  |
| Number of subjects analysed       | 81 <sup>[1]</sup>           | 86 <sup>[2]</sup>           | 83 <sup>[3]</sup>   |  |
| Units: Percentage of Participants |                             |                             |                     |  |
| number (confidence interval 95%)  | 96.3 (89.6 to 99.2)         | 98.8 (93.7 to 100)          | 95.2 (88.1 to 98.7) |  |

Notes:

- [1] - Two participants with indeterminate or missing responses are excluded from the analysis
- [2] - One participant with indeterminate or missing responses is excluded from the analysis
- [3] - Two participants with indeterminate or missing responses are excluded from the analysis

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Relebactam 250 mg - Placebo: Treatment Difference |
| Statistical analysis description:<br>Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without |   |



stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 164   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | < 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 1.1   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.2  |
| upper limit                             | 8.6   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Treatment Difference |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 169   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | < 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 3.7   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2  |
| upper limit                             | 10.8  |

**Primary: Percentage of participants with an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values that are greater than or equal to 5X the upper limit of normal (ULN)**

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values that are greater than or equal to 5X the upper limit of normal (ULN) |
|-----------------|---|

End point description:

Pre-specified events of interest were confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 X ULN as a result of within-protocol-specific testing or unscheduled testing. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

| <b>End point values</b>           | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 1.7                               | 0                                 | 1.8                  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Relebactam 250 mg - Placebo: Percent Difference |
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other <sup>[4]</sup>                            |
| P-value                                 | = 0.979   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.7  |
| upper limit                             | 4.5   |

Notes:

[4] - The analysis type is a traditional test for a non-zero difference.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Relebactam 125 mg - Placebo: Percent Difference |
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other <sup>[5]</sup>                            |
| P-value                                 | = 0.153   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.2  |
| upper limit                             | 1.5   |

Notes:

[5] - The analysis type is a traditional test for a non-zero difference.

### Primary: Percentage of participants with elevated AST or ALT laboratory values that

**are greater than or equal to 3X the ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with elevated AST or ALT laboratory values that are greater than or equal to 3X the ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN |
|-----------------|--|

End point description:

Pre-specified events of interest were confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 3 X ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN, as a result of within-protocol-specific testing or unscheduled testing. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 0.9                               | 0                                 | 0                    |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Relebactam 250 mg - Placebo: Percent Difference |
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other <sup>[6]</sup>                            |
| P-value                                 | = 0.324   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.9   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.4  |
| upper limit                             | 4.7   |

Notes:

[6] - The analysis type is a traditional test for a non-zero difference.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Percent Difference |
| Comparison groups                 | Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 230                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[7]</sup>   |
| P-value                                 | > 0.999                |
| Method                                  | Miettinen and Nurminen |
| Parameter estimate                      | Percentage Difference  |
| Point estimate                          | 0                      |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -3.3                   |
| upper limit                             | 3.2                    |

Notes:

[7] - The analysis type is a traditional test for a non-zero difference.

### Primary: Percentage of participants with any adverse event (AE)

|  |  |
|--|--|
| End point title  | Percentage of participants with any adverse event (AE) |
| End point description:   |  |
| An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Up to 14 days following completion of all study therapy (up to Day 28)   |  |

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 48.7                              | 47.4                              | 41.2                 |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Relebactam 250 mg - Placebo: Treatment Difference |
| Statistical analysis description:  |   |
| Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups  | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 231                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | 7.5                   |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -5.4                  |
| upper limit                             | 20.1                  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: Treatment Difference |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 6.2   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -6.7  |
| upper limit   | 18.8  |

|   |   |
|---|---|
| <b>Primary: Percentage of participants with any serious adverse event (SAE)</b>   |   |
| End point title   | Percentage of participants with any serious adverse event (SAE) |
| End point description:<br>A SAE is any AE occurring at any dose that is life threatening; results in a persistent or significant disability/incapacity; prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; or results in death. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received. |   |
| End point type  | Primary   |
| End point timeframe:<br>Up to 14 days following completion of all study therapy (up to Day 28)  |   |

| <b>End point values</b>           | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 3.4                               | 9.5                               | 7                    |  |

## Statistical analyses

| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: Treatment Difference |
|---|---|
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | -3.6  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -10.3   |
| upper limit   | 2.4   |

| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: Treatment Difference |
|---|---|
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 2.5   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -5  |
| upper limit   | 10.1  |

## Primary: Percentage of participants with any drug-related AE

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with any drug-related AE |
|-----------------|---|

**End point description:**

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. A drug-related AE is an AE determined by the investigator to be possibly, probably or definitely related to drug treatment. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| Up to 14 days following completion of all study therapy (up to Day 28) |         |

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 13.7                              | 13.8                              | 9.6                  |  |

**Statistical analyses**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: Treatment Difference |
|-----------------------------------|---|

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 4   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.5  |
| upper limit                             | 12.7  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Treatment Difference |
|-----------------------------------|---|

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 230                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | 4.1                   |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -4.4                  |
| upper limit                             | 12.8                  |

### Primary: Percentage of participants with any serious drug-related AE

|                        |  |
|------------------------|--|
| End point title        | Percentage of participants with any serious drug-related AE  |
| End point description: | A SAE is any AE occurring at any dose that is life threatening; results in a persistent or significant disability/incapacity; prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; or results in death. A drug-related SAE is a SAE determined by the investigator to be possibly, probably or definitely related to drug treatment. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received. |
| End point type         | Primary  |
| End point timeframe:   | Up to 42 days following completion of all study therapy (up to Day 56)   |

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 0.9                               | 0                                 | 0.9                  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Relebactam 250 mg - Placebo: Treatment Difference  |
| Statistical analysis description:       | Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL  |
| Number of subjects included in analysis | 231  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| Parameter estimate                      | Percentage Difference  |
| Point estimate                          | 0  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4      |
| upper limit         | 3.9     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Treatment Difference |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.9  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4.8    |
| upper limit         | 2.4     |

### Primary: Percentage of participants who discontinued IV study therapy due to an AE

|                 |   |
|-----------------|---|
| End point title | Percentage of participants who discontinued IV study therapy due to an AE |
|-----------------|---|

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. AEs assessed by the investigator that caused discontinuation of participant treatment are presented. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days post initiation of IV study therapy

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 0.9                               | 4.3                               | 2.6                  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: Treatment Difference |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | -1.8  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -6.7  |
| upper limit   | 2.3   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: Treatment Difference |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 1.7   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -3.7  |
| upper limit   | 7.4   |

## Primary: Percentage of participants who discontinued IV study therapy due to a drug-related AE

|                 |   |
|-----------------|---|
| End point title | Percentage of participants who discontinued IV study therapy due to a drug-related AE |
|-----------------|---|

### End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or

intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. A drug-related AE is an AE determined by the investigator to be possibly, probably or definitely related to drug treatment. Drug-related AEs assessed by the investigator that caused discontinuation of participant treatment are presented. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

|   |         |
|---|---------|
| End point type                                    | Primary |
| End point timeframe:                              |         |
| Up to 14 days post initiation of IV study therapy |         |

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           | 0                                 | 0.9                               | 2.6                  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Relebactam 250 mg - Placebo: Treatment Difference |
| Statistical analysis description:  |   |
| Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups  | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis  | 231   |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | other   |
| Parameter estimate   | Percentage Difference                             |
| Point estimate   | -2.6  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -7.5  |
| upper limit  | 0.6   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Relebactam 125 mg - Placebo: Treatment Difference |
| Statistical analysis description:  |   |
| Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups  | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 230                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | -1.8                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -6.7                  |
| upper limit                             | 2.4                   |

**Primary: Percentage of participants with AEs with incidence of  $\geq 4$  participants in one treatment group**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with AEs with incidence of $\geq 4$ participants in one treatment group |
|-----------------|--|

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. AE preferred terms with incidence greater than or equal to 4 in one treatment group are presented. AEs preferred terms which did not achieve this threshold are not reported. AE preferred terms are based on MedDRA version 17.0. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days post initiation of IV study therapy (up to Day 28)

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           |                                   |                                   |                      |  |
| Diarrhoea                         | 6                                 | 6                                 | 4.4                  |  |
| Nausea                            | 6.8                               | 7.8                               | 7                    |  |
| Vomiting                          | 6                                 | 7.8                               | 2.6                  |  |
| Post-operative wound infection    | 2.6                               | 1.7                               | 4.4                  |  |
| Seroma                            | 0.9                               | 4.3                               | 0                    |  |
| ALT increased                     | 4.3                               | 4.3                               | 3.5                  |  |
| AST increased                     | 4.3                               | 4.3                               | 2.6                  |  |
| Lipase increased                  | 2.6                               | 1.7                               | 3.5                  |  |
| Hypertension                      | 0                                 | 2.6                               | 3.5                  |  |

## Statistical analyses

| Statistical analysis title  | Relebactam 250 mg - Placebo: % Diff. - Diarrhoea |
|---|--|
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |  |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL  |
| Number of subjects included in analysis   | 231  |
| Analysis specification  | Pre-specified                                    |
| Analysis type   | other  |
| Parameter estimate  | Percentage Difference                            |
| Point estimate  | 1.6  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -4.7   |
| upper limit   | 8.1  |

| Statistical analysis title  | Relebactam 125 mg - Placebo: % Diff. - Diarrhoea |
|---|--|
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |  |
| Comparison groups   | Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL  |
| Number of subjects included in analysis   | 230  |
| Analysis specification  | Pre-specified                                    |
| Analysis type   | other  |
| Parameter estimate  | Percentage Difference                            |
| Point estimate  | 1.6  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -4.6   |
| upper limit   | 8.2  |

| Statistical analysis title  | Relebactam 250 mg - Placebo: % Diff. - Nausea   |
|---|---|
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -0.2  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -7.3    |
| upper limit         | 6.9     |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Difference - Nausea |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.7   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.5  |
| upper limit                             | 8   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Vomiting |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 3.4   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.3  |
| upper limit                             | 9.6   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - Vomiting |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 230                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | 5.1                   |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -0.7                  |
| upper limit                             | 11.8                  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Post.inf. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -7.6  |
| upper limit                             | 3.5   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - Post.inf. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -2.7  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -8.4  |
| upper limit                             | 2.2   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Difference - Seroma |
|-----------------------------------|--|

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.9   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.4  |
| upper limit                             | 4.7   |

**Statistical analysis title**

Relebactam 125 mg - Placebo: % Difference - Seroma

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 4.3   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1   |
| upper limit                             | 9.7   |

**Statistical analysis title**

Relebactam 250 mg - Placebo: % Diff. - ALT inc.

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.8   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5  |
| upper limit                             | 6.6   |



|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - ALT inc. |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | 0.8   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -4.9  |
| upper limit   | 6.7   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: % Diff. - AST inc. |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | 1.6   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -3.7  |
| upper limit   | 7.3   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - AST inc. |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | 1.7   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.7    |
| upper limit         | 7.4     |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff.-Lip. inc. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.9  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.5  |
| upper limit                             | 4.2   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff.-Lip. inc. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -7.2  |
| upper limit                             | 3   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Hyp. |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 231                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | -3.5                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -8.7                  |
| upper limit                             | -0.3                  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - Hyp.     |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -0.9  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -6.4  |
| upper limit   | 4.3   |

### **Primary: Percentage of participants with predefined limit of change (PDLC) with incidence of $\geq 4$ participants in one treatment group**

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with predefined limit of change (PDLC) with incidence of $\geq 4$ participants in one treatment group <sup>[8]</sup> |
|-----------------|---|

End point description:

PDLC are presented based on values from the following laboratory tests on serum: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bil), and alkaline phosphatase (AP). Results are presented for PDLC from tests with reported incidence greater than or equal to 4 participants in one treatment group. Laboratory tests which did not achieve the PDLC threshold are not reported. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics are provided. Statistical comparisons between arms were not performed for this primary endpoint.

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (not applicable)           |                                   |                                   |                      |  |
| ALT >2.5-5.0 X Baseline           | 3.6                               | 2.6                               | 9.1                  |  |
| ALT >5.0 X Baseline               | 4.5                               | 6.1                               | 3.6                  |  |
| AST >2.5-5.0 X Baseline           | 14.5                              | 14                                | 9.2                  |  |
| AP >2.5-5.0 X Baseline            | 6.3                               | 2.6                               | 5.5                  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of participants with system organ class (SOC) AE incidence of $\geq 4$ participants in one treatment group

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with system organ class (SOC) AE incidence of $\geq 4$ participants in one treatment group |
|-----------------|---|

End point description:

A SOC is the highest level of terminology used to describe disorders of the human body, and distinguishes by either anatomical or physiological systems, disease origin or purpose. SOC AE incidence greater than or equal to 4 in one treatment group are presented. SOC AE incidence which did not achieve this threshold are not reported. SOC are based on MedDRA version 17.0. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

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

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

| End point values                            | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|---|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                          | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed                 | 117                               | 116                               | 114                  |  |
| Units: Percentage of participants           |                                   |                                   |                      |  |
| number (not applicable)                     |                                   |                                   |                      |  |
| Blood and lymphatic system disorders        | 4.3                               | 0.9                               | 5.3                  |  |
| Cardiac disorders                           | 2.6                               | 3.4                               | 2.6                  |  |
| Gastrointestinal disorders                  | 18.8                              | 17.2                              | 13.2                 |  |
| General disorders admin. site conditions    | 7.7                               | 5.2                               | 3.5                  |  |
| Infections and infestations                 | 11.1                              | 7.8                               | 7                    |  |
| Injury, poisoning, procedural complications | 4.3                               | 6.9                               | 5.3                  |  |
| Investigations                              | 11.1                              | 10.3                              | 12.3                 |  |
| Nervous system disorders                    | 1.7                               | 3.4                               | 4.4                  |  |
| Psychiatric disorders                       | 3.4                               | 3.4                               | 3.5                  |  |
| Renal and urinary disorders                 | 1.7                               | 1.7                               | 3.5                  |  |

|  |     |     |     |  |
|--|-----|-----|-----|--|
| Respiratory, thoracic, mediastinal disorders | 1.7 | 4.3 | 6.1 |  |
| Skin, subcutaneous tissue disorders          | 4.3 | 1.7 | 1.8 |  |
| Vascular disorders                           | 2.6 | 6   | 6.1 |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Relebactam 250 mg - Placebo: % Diff. - Blood    |
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -7.3  |
| upper limit                             | 5.1   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - Blood    |
| Statistical analysis description:   |   |
| Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -4.4  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -10.3   |
| upper limit   | 0.1   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Relebactam 250 mg - Placebo: % Diff.-Card. dis. |
| Statistical analysis description:  |   |
| Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups  | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 231                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | -1                    |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -5.2                  |
| upper limit                             | 5                     |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. -Card. dis. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.8   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.5  |
| upper limit                             | 6.3   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - GI Dis. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 5.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -3.9  |
| upper limit                             | 15.3  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - GI Dis. |
|-----------------------------------|--|

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 4.1   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.4  |
| upper limit                             | 13.6  |

---

**Statistical analysis title**

Relebactam 250 mg - Placebo: % Diff. -Gen.dis.

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 4.2   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2  |
| upper limit                             | 11  |

---

**Statistical analysis title**

Relebactam 125 mg - Placebo: % Diff. -Gen.dis.

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 1.7   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.2  |
| upper limit                             | 7.8   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: % Diff. - Infct.   |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | 4.1   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -3.6  |
| upper limit   | 12  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - Infct.   |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | 0.7   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -6.5  |
| upper limit   | 8   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: % Diff. -Inj.Pois. |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -1  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -7.3    |
| upper limit         | 5.1     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. -Inj.Pois. |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 1.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5  |
| upper limit                             | 8.5   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Inv. |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.2  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -9.8  |
| upper limit                             | 7.4   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - Inv. |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 230                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | -1.9                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -10.5                 |
| upper limit                             | 6.5                   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Nerv. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -2.7  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -8.4  |
| upper limit                             | 2.2   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - Nerv. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.9  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.9  |
| upper limit                             | 4.7   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Psych. |
|-----------------------------------|---|

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.1  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.7  |
| upper limit                             | 5.4   |

---

**Statistical analysis title**

Relebactam 125 mg - Placebo: % Diff. - Psych.

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.1  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.7  |
| upper limit                             | 5.5   |

---

**Statistical analysis title**

Relebactam 250 mg - Placebo: % Diff. - Renal

---

**Statistical analysis description:**

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Placebo + IPM/CIL v Relebactam 250 mg + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -7.2  |
| upper limit                             | 3   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - Renal    |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -1.8  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -7.2  |
| upper limit   | 3   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: % Diff.- Resp.     |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 231   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -4.4  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -10.7   |
| upper limit   | 0.7   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff.- Resp.     |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -1.8  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -8.4    |
| upper limit         | 4.4     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Skin |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 2.5   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.4  |
| upper limit                             | 8.1   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: % Diff. - Skin |
|-----------------------------------|---|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 230   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.7  |
| upper limit                             | 4.5   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: % Diff. - Vasc. |
|-----------------------------------|--|

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 231                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Percentage Difference |
| Point estimate                          | -3.6                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -9.9                  |
| upper limit                             | 2                     |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: % Diff. - Vasc.    |
| Statistical analysis description:<br>Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis   | 230   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Percentage Difference                           |
| Point estimate  | -0.1  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -6.9  |
| upper limit   | 6.6   |

**Secondary: Percentage of participants with a favorable clinical response at completion of IV study therapy in participants who have imipenem-resistant, gram-negative cIAI infections.**

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with a favorable clinical response at completion of IV study therapy in participants who have imipenem-resistant, gram-negative cIAI infections. |
|-----------------|---|

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; (4) received  $\geq 96$  hours of IV study therapy; and (5) had imipenem-resistant, gram negative cIAI infections.

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

End point timeframe:

4 to 14 days post initiation of IV study therapy (up to postrandomization Day 14).

| End point values                  | Relebactam 250 mg + IPM/CIL | Relebactam 125 mg + IPM/CIL | Placebo + IPM/CIL  |  |
|-----------------------------------|-----------------------------|-----------------------------|--------------------|--|
| Subject group type                | Reporting group             | Reporting group             | Reporting group    |  |
| Number of subjects analysed       | 14 <sup>[9]</sup>           | 9 <sup>[10]</sup>           | 11 <sup>[11]</sup> |  |
| Units: Percentage of participants |                             |                             |                    |  |
| number (confidence interval 95%)  | 100 (76.8 to 100)           | 100 (66.4 to 100)           | 100 (71.5 to 100)  |  |

Notes:

[9] - Had imipenem-resistant, gram negative cIAI infections.

[10] - Had imipenem-resistant, gram negative cIAI infections.

[11] - Had imipenem-resistant, gram negative cIAI infections.

## Statistical analyses

| Statistical analysis title              | Relebactam 250 mg - Placebo: Treatment Difference |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis | 25  |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | > 0.999   |
| Method                                  | Fisher exact                                      |
| Parameter estimate                      | Percentage Difference                             |
| Point estimate                          | 0   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0   |
| upper limit                             | 0   |

| Statistical analysis title              | Relebactam 125 mg - Placebo: Treatment Difference |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis | 20  |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | > 0.999   |
| Method                                  | Fisher exact                                      |
| Parameter estimate                      | Percentage Difference                             |
| Point estimate                          | 0   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0   |
| upper limit                             | 0   |

## Secondary: Percentage of participants with a favorable clinical response at early follow-up

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with a favorable clinical response at |
|-----------------|--|

## End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received  $\geq 96$  hours of IV study therapy.

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

## End point timeframe:

Up to 9 days following completion of all study therapy (up to Day 23)

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL   |  |
|-----------------------------------|-----------------------------------|-----------------------------------|------------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group        |  |
| Number of subjects analysed       | 79                                | 86                                | 81                     |  |
| Units: Percentage of participants |                                   |                                   |                        |  |
| number (confidence interval 95%)  | 94.9 (87.5 to<br>98.6)            | 94.2 (87 to<br>98.1)              | 96.3 (89.6 to<br>99.2) |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Relebactam 250 mg - Placebo: Treatment Difference |
|----------------------------|---|

## Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 160   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | = 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.4  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -9.1  |
| upper limit                             | 6   |

|                            |   |
|----------------------------|---|
| Statistical analysis title | Relebactam 125 mg - Placebo: Treatment Difference |
|----------------------------|---|

## Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|



|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 167                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | non-inferiority        |
| P-value                                 | = 0.002                |
| Method                                  | Miettinen and Nurminen |
| Parameter estimate                      | Percentage Difference  |
| Point estimate                          | -2.1                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -9.7                   |
| upper limit                             | 5.3                    |

### Secondary: Percentage of participants with a favorable microbiological response at completion of IV study therapy

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with a favorable microbiological response at completion of IV study therapy |
|-----------------|--|

End point description:

A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

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

End point timeframe:

Up to 14 days post-initiation of IV study therapy (up to postrandomization Day 14)

| End point values                  | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 83                                | 86                                | 84                   |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (confidence interval 95%)  | 97.6 (91.6 to 99.7)               | 100 (95.8 to 100)                 | 97.6 (91.7 to 99.7)  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Relebactam 250 mg - Placebo: Treatment Difference |
|----------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Two participants with indeterminate or missing response were excluded from the analysis.

|                   |   |
|-------------------|---|
| Comparison groups | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
|-------------------|---|

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 167                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | non-inferiority        |
| P-value                                 | < 0.001                |
| Method                                  | Miettinen and Nurminen |
| Parameter estimate                      | Percentage Difference  |
| Point estimate                          | 0                      |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -6.3                   |
| upper limit                             | 6.2                    |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Treatment Difference |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Two participants with indeterminate or missing response were excluded from the analysis.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 170   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | < 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 2.4   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2  |
| upper limit                             | 8.3   |

### **Secondary: Percentage of participants with a favorable microbiological response at early follow-up**

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with a favorable microbiological response at early follow-up |
|-----------------|---|

End point description:

A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

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

End point timeframe:

Up to 9 days following completion of all study therapy (up to Day 23)

| <b>End point values</b>           | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL   |  |
|-----------------------------------|-----------------------------------|-----------------------------------|------------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group        |  |
| Number of subjects analysed       | 78                                | 82                                | 80                     |  |
| Units: Percentage of participants |                                   |                                   |                        |  |
| number (confidence interval 95%)  | 97.4 (91 to<br>99.7)              | 97.6 (91.5 to<br>99.7)            | 97.5 (91.3 to<br>99.7) |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Relebactam 250 mg - Placebo: Treatment Difference |
|-----------------------------------|---|
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 158   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | < 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -0.1  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.7  |
| upper limit                             | 6.4   |

| <b>Statistical analysis title</b> | Relebactam 125 mg - Placebo: Treatment Difference |
|-----------------------------------|---|
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 162   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | < 0.001   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | 0.1   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.3  |
| upper limit                             | 6.5   |

## Secondary: Percentage of participants with a favorable clinical response at late follow-up

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with a favorable clinical response at late follow-up |
|-----------------|---|

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received  $\geq 96$  hours of IV study therapy.

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

End point timeframe:

Up to 42 days following completion of all study therapy (up to Day 56)

| End point values                  | Relebactam 250 mg + IPM/CIL | Relebactam 125 mg + IPM/CIL | Placebo + IPM/CIL   |  |
|-----------------------------------|-----------------------------|-----------------------------|---------------------|--|
| Subject group type                | Reporting group             | Reporting group             | Reporting group     |  |
| Number of subjects analysed       | 79                          | 85                          | 79                  |  |
| Units: Percentage of participants |                             |                             |                     |  |
| number (confidence interval 95%)  | 93.7 (85.8 to 97.9)         | 95.3 (88.4 to 98.7)         | 94.9 (87.5 to 98.6) |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Relebactam 250 mg - Placebo: Treatment Difference |
|----------------------------|---|

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

|   |   |
|---|---|
| Comparison groups                       | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL |
| Number of subjects included in analysis | 158   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| P-value                                 | = 0.002   |
| Method                                  | Miettinen and Nurminen                          |
| Parameter estimate                      | Percentage Difference                           |
| Point estimate                          | -1.3  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -9.6  |
| upper limit                             | 6.9   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: Treatment Difference |
| Statistical analysis description:<br>Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 164   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | non-inferiority                                   |
| P-value   | < 0.001   |
| Method  | Miettinen and Nurminen                            |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 0.4   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -7.2  |
| upper limit   | 8.2   |

### Secondary: Percentage of participants with a favorable microbiological response at late follow-up

|   |  |
|---|--|
| End point title   | Percentage of participants with a favorable microbiological response at late follow-up |
| End point description:<br>A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to 42 days following completion of all study therapy up to Day 56)   |  |

| <b>End point values</b>           | Relebactam<br>250 mg +<br>IPM/CIL | Relebactam<br>125 mg +<br>IPM/CIL | Placebo +<br>IPM/CIL |  |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------------|--|
| Subject group type                | Reporting group                   | Reporting group                   | Reporting group      |  |
| Number of subjects analysed       | 78                                | 81                                | 78                   |  |
| Units: Percentage of participants |                                   |                                   |                      |  |
| number (confidence interval 95%)  | 96.2 (89.2 to 99.2)               | 97.5 (91.4 to 99.7)               | 96.2 (89.2 to 99.2)  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 250 mg - Placebo: Treatment Difference |
| Statistical analysis description:   |   |
| Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis. |   |
| Comparison groups   | Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 156   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | non-inferiority                                   |
| P-value   | < 0.001   |
| Method  | Miettinen and Nurminen                            |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 0   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -7.4  |
| upper limit   | 7.4   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Relebactam 125 mg - Placebo: Treatment Difference |
| Statistical analysis description:   |   |
| Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis. |   |
| Comparison groups   | Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL   |
| Number of subjects included in analysis   | 159   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | non-inferiority                                   |
| P-value   | < 0.001   |
| Method  | Miettinen and Nurminen                            |
| Parameter estimate  | Percentage Difference                             |
| Point estimate  | 1.4   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -5.2  |
| upper limit   | 8.6   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During study therapy and the protocol-specified follow-up period following end of study therapy (up to 28 days for non-serious AEs and up to 56 days for serious drug-related AEs)

Adverse event reporting additional description:

Population analyzed is all randomized participants who received at least one dose of IV study therapy. Participants with All-Cause Mortality were determined by the investigator to include some participants discontinued due to an adverse event, and progressive disease.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Relebactam 250 mg + IPM/CIL |
|-----------------------|-----------------------------|

Reporting group description:

Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Relebactam 125 mg + IPM/CIL |
|-----------------------|-----------------------------|

Reporting group description:

Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo + IPM/CIL |
|-----------------------|-------------------|

Reporting group description:

Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

| Serious adverse events  | Relebactam 250 mg + IPM/CIL | Relebactam 125 mg + IPM/CIL | Placebo + IPM/CIL |
|---|-----------------------------|-----------------------------|-------------------|
| Total subjects affected by serious adverse events                   |                             |                             |                   |
| subjects affected / exposed   | 4 / 117 (3.42%)             | 11 / 116 (9.48%)            | 8 / 114 (7.02%)   |
| number of deaths (all causes)                                       | 0                           | 3                           | 0                 |
| number of deaths resulting from adverse events                      | 0                           | 3                           | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                             |                   |
| Benign gastrointestinal neoplasm                                    |                             |                             |                   |
| subjects affected / exposed   | 0 / 117 (0.00%)             | 1 / 116 (0.86%)             | 0 / 114 (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             |
| Mucinous adenocarcinoma of appendix                                 |                             |                             |                   |
| subjects affected / exposed   | 0 / 117 (0.00%)             | 0 / 116 (0.00%)             | 1 / 114 (0.88%)   |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 0                       | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                       | 0 / 0             |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Post procedural bile leak                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Procedural pain                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound dehiscence                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound evisceration                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 117 (0.85%) | 0 / 116 (0.00%) | 0 / 114 (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           |
| Suture rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Cardiac failure chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 117 (0.85%) | 0 / 116 (0.00%) | 0 / 114 (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           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Ventricular fibrillation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Nervous system disorders                        |                 |                 |                 |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Thrombocytosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Ileus paralytic                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 117 (0.85%) | 0 / 116 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Pancreatitis acute                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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                         |                 |                 |                 |
| Cholelithiasis obstructive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 0 / 116 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung consolidation                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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 / 117 (0.00%) | 0 / 116 (0.00%) | 2 / 114 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Renal failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal abscess                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile infection                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Liver abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 117 (0.85%) | 0 / 116 (0.00%) | 0 / 114 (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           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (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           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 117 (0.00%) | 1 / 116 (0.86%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 1 / 1           |

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

| <b>Non-serious adverse events</b>                     | Relebactam 250 mg<br>+ IPM/CIL | Relebactam 125 mg<br>+ IPM/CIL | Placebo + IPM/CIL |
|---|--------------------------------|--------------------------------|-------------------|
| Total subjects affected by non-serious adverse events |                                |                                |                   |
| subjects affected / exposed                           | 16 / 117 (13.68%)              | 15 / 116 (12.93%)              | 13 / 114 (11.40%) |
| Gastrointestinal disorders                            |                                |                                |                   |
| Diarrhoea   |                                |                                |                   |
| subjects affected / exposed                           | 7 / 117 (5.98%)                | 6 / 116 (5.17%)                | 5 / 114 (4.39%)   |
| occurrences (all)                                     | 8                              | 6                              | 5                 |
| Nausea  |                                |                                |                   |
| subjects affected / exposed                           | 8 / 117 (6.84%)                | 9 / 116 (7.76%)                | 8 / 114 (7.02%)   |
| occurrences (all)                                     | 9                              | 9                              | 9                 |
| Vomiting  |                                |                                |                   |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 7 / 117 (5.98%) | 9 / 116 (7.76%) | 3 / 114 (2.63%) |
| occurrences (all)           | 7               | 9               | 3               |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported