



Clinical trial results:

A multi-center, randomized, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects with Clostridium difficile-associated diarrhea (CDAD)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-002508-15 |
| Trial protocol | CZ BE HU SK GR HR |
| Global end of trial date | 02 May 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 13 May 2018 |
| First version publication date | 13 May 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-061A302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01983683 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.com |
| Scientific contact | clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.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 | 13 June 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 May 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether the clinical response after 10-day oral administration of cadazolid is non-inferior to oral vancomycin in subjects with CDAD.

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21 (adapt to the countries where the trial was conducted), and with the ethical principles laid down in the Declaration of Helsinki

Background therapy: -

Evidence for comparator:

The comparator, vancomycin, is approved in Europe and in the US for the treatment of mild-moderate CDAD

| | |
|---|------------------|
| Actual start date of recruitment | 13 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United States: 220 |
| Country: Number of subjects enrolled | Canada: 31 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Croatia: 17 |
| Country: Number of subjects enrolled | Czech Republic: 44 |
| Country: Number of subjects enrolled | Greece: 47 |
| Country: Number of subjects enrolled | Hungary: 33 |
| Country: Number of subjects enrolled | Romania: 89 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Argentina: 12 |
| Country: Number of subjects enrolled | Brazil: 37 |
| Country: Number of subjects enrolled | Chile: 8 |
| Country: Number of subjects enrolled | Israel: 43 |
| Country: Number of subjects enrolled | Korea, Republic of: 12 |
| Worldwide total number of subjects | 609 |
| EEA total number of subjects | 246 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 301 |
| From 65 to 84 years | 308 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

1128 patients at 105 sites in 15 countries were screened, among whom 631 were randomized at 96 sites in 14 countries worldwide.

Pre-assignment

Screening details:

Among the 631 subjects randomized, 22 were excluded from all the analyses due to potential data integrity issues resulting in 609 total participants considered for the analyses. From the 22 excluded patients no serious adverse events (AEs) or study drug discontinuation information were reported. All reported AEs were mild or moderate in intensity.

Period 1

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

Blinding implementation details:

The sponsor staff (except Global Drug Safety in case of SUSAR) and CRO staff (except people responsible for safety report distribution or for bioanalytical analyses of cadazolid) remained blinded to the treatment until unblinding after study closure

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cadazolid |

Arm description:

Subjects with Clostridium difficile-associated diarrhea (CDAD) received oral cadazolid 250 mg twice daily (bid) and oral vancomycin-matching placebo 4 times a day (qid) for 10 days. Subjects were followed up for 30 days after the last dose of cadazolid. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up)

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cadazolid |
| Investigational medicinal product code | ACT-179811 |
| Other name | |
| Pharmaceutical forms | Granules for oral solution in sachet |
| Routes of administration | Oral use |

Dosage and administration details:

Granules to be reconstituted as a suspension prior to oral administration, supplied at a dose of 250 mg

| | |
|--|-----------------------------|
| Investigational medicinal product name | Vancomycin-matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Capsule identical to vancomycin-capsule but without active substance

| | |
|------------------|------------|
| Arm title | Vancomycin |
|------------------|------------|

Arm description:

Subjects with CDAD received oral vancomycin 125 mg qid and oral cadazolid-matching placebo bid for 10 days. Subjects were followed up for 30 day after the last dose of vancomycin. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up)

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Vancomycin |
| Investigational medicinal product code | |
| Other name | Vancocin® |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Each capsule contains 125 mg of vancomycin

| | |
|--|--|
| Investigational medicinal product name | Cadazolid-matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules for oral suspension in sachet |
| Routes of administration | Oral use |

Dosage and administration details:

Granules without active substance, to be reconstituted as a suspension prior to oral administration

| Number of subjects in period 1 | Cadazolid | Vancomycin |
|---------------------------------------|-----------|------------|
| Started | 298 | 311 |
| Completed | 260 | 260 |
| Not completed | 38 | 51 |
| Adverse event, serious fatal | 11 | 15 |
| Consent withdrawn by subject | 14 | 18 |
| Physician decision | 8 | 9 |
| Sponsor Decision | 1 | 1 |
| Lost to follow-up | 4 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | Cadazolid |
| Reporting group description: Subjects with Clostridium difficile-associated diarrhea (CDAD) received oral cadazolid 250 mg twice daily (bid) and oral vancomycin-matching placebo 4 times a day (qid) for 10 days. Subjects were followed up for 30 days after the last dose of cadazolid. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up) | |
| Reporting group title | Vancomycin |
| Reporting group description: Subjects with CDAD received oral vancomycin 125 mg qid and oral cadazolid-matching placebo bid for 10 days. Subjects were followed up for 30 day after the last dose of vancomycin. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up) | |

| Reporting group values | Cadazolid | Vancomycin | Total |
|------------------------|-----------|------------|-------|
| Number of subjects | 298 | 311 | 609 |
| Age categorical | | | |
| Units: Subjects | | | |
| 18-64 years | 143 | 158 | 301 |
| 65-74 years | 66 | 61 | 127 |
| 75 years and older | 89 | 92 | 181 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.8 | 62.0 | |
| standard deviation | ± 18.6 | ± 17.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 194 | 189 | 383 |
| Male | 104 | 122 | 226 |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Cadazolid |
|-----------------------|-----------|

Reporting group description:

Subjects with Clostridium difficile-associated diarrhea (CDAD) received oral cadazolid 250 mg twice daily (bid) and oral vancomycin-matching placebo 4 times a day (qid) for 10 days. Subjects were followed up for 30 days after the last dose of cadazolid. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up)

| | |
|-----------------------|------------|
| Reporting group title | Vancomycin |
|-----------------------|------------|

Reporting group description:

Subjects with CDAD received oral vancomycin 125 mg qid and oral cadazolid-matching placebo bid for 10 days. Subjects were followed up for 30 day after the last dose of vancomycin. Subjects who had a first recurrence of CDAD during the follow-up period were offered to enter a re-treatment extension period with cadazolid (10 days of cadazolid + 30-day follow up)

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | Modified intent-to-treat set (mITT) |
|----------------------------|-------------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All randomized subjects who have received at least one dose of study treatment and had a confirmed diagnosis of CDAD

| | |
|----------------------------|------------------------|
| Subject analysis set title | Per protocol set (PPS) |
|----------------------------|------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

All subjects from the mITT and without protocol deviations that might affect the evaluation of the effect of the study drug on the primary variable.

| | |
|----------------------------|-----------------|
| Subject analysis set title | Safety set (SS) |
|----------------------------|-----------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All randomized subjects who received at least one dose of study treatment and analyzed based on the actual treatment received

Primary: Clinical Cure Rate (CCR) in the modified intent-to-treat population

| | |
|-----------------|---|
| End point title | Clinical Cure Rate (CCR) in the modified intent-to-treat population |
|-----------------|---|

End point description:

Clinical Cure is defined as: • Resolution of Diarrhea (ROD) (≤ 3 unformed bowel movement (UBM) per day for at least 2 consecutive days) on study treatment and maintained for 2 days after end-of-treatment (EOT), AND • No additional antimicrobial treatment active against Clostridium difficile-associated diarrhea (CDAD) or fecal microbiota transplant (FMT) between first dose of study drug and 2 days after EOT (inclusive). CCR is the percentage of subjects with Clinical Cure. Analyses are performed on two analysis sets. Results on the modified intent-to-treat set (mITT) are reported below.

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

End point timeframe:

Up to Day 12 on average (end-of-treatment + 2 days)

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 301 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of participants | 81 (76.1 to 85.1) | 85.7 (81.3 to 89.2) | | |

Statistical analyses

| Statistical analysis title | Main analysis |
|---|----------------------------------|
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | -4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.7 |
| upper limit | 1.3 |

Notes:

[1] - Non-inferiority of CCR for cadazolid versus vancomycin is demonstrated if the lower limit of the 95% confidence interval (CI) is above -10. CIs are estimated using the Wilson's score method.

| Statistical analysis title | Sensitivity analysis |
|--|----------------------------------|
| Statistical analysis description: | |
| Sensitivity analysis with imputation for a single day with missing UBM data between one day before end-of-treatment (EOT) and 2 days after EOT | |
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | -3.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.6 |
| upper limit | 2.3 |

Notes:

[2] - Non-inferiority of CCR for cadazolid versus vancomycin is demonstrated if the lower limit of the 95% confidence interval (CI) is above -10%. CIs are estimated using the Wilson's score method.

Primary: Clinical Cure Rate (CCR) in the per-protocol population

| End point title | Clinical Cure Rate (CCR) in the per-protocol population |
|-----------------|---|
|-----------------|---|

End point description:

Clinical Cure (CC) is defined as: • Resolution of Diarrhea (≤ 3 unformed bowel movement per day for at least 2 consecutive days) on study treatment and maintained for 2 days after end-of-treatment (EOT), AND • No additional antimicrobial treatment active against Clostridium difficile-associated diarrhea

(CDAD) or fecal microbiota transplant between first dose of study drug and 2 days after EOT. CCR is the percentage of subjects with Clinical Cure. Analyses are performed on two analysis sets. Results on the per-protocol set (PPS) are reported below.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to Day 12 on average (end-of-treatment + 2 days) | |

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 259 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of participants | 86.6 (81.8 to 90.3) | 91.5 (87.5 to 94.3) | | |

Statistical analyses

| Statistical analysis title | Main analysis |
|---|----------------------------------|
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | -4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | 0.6 |

Notes:

[3] - Non-inferiority of CCR for cadazolid versus vancomycin is demonstrated if the lower limit of the 95% confidence interval (CI) is above -10%. CIs are estimated using the Wilson's score method.

Secondary: Sustained Cure Rate (SCR) in the modified intent-to-treat population

| | |
|--|--|
| End point title | Sustained Cure Rate (SCR) in the modified intent-to-treat population |
| End point description: | |
| Sustained Cure is defined for each subject having Clinical Cure and no recurrence. SCR is the percentage of subjects with Sustained Cure. The main analysis is performed on the modified intent-to-treat set (mITT). | |
| End point type | Secondary |
| End point timeframe: | |
| Between Day 38 and Day 42 on average (end-of-treatment + 28-32 days) | |

| End point values | Cadazolid | Vancomycin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 301 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of subjects | 63.4 (57.8 to 68.8) | 61.8 (56.2 to 67.1) | | |

Statistical analyses

| Statistical analysis title | Main analysis |
|---|----------------------------------|
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | 1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.1 |
| upper limit | 9.4 |

Notes:

[4] - Superiority of cadazolid versus vancomycin is demonstrated if the lower limit of the 95% confidence interval (CI) is above zero. CIs are estimated using the Wilson's score method.

Secondary: Kaplan-Meier estimates for resolution of diarrhea

| | |
|---|---|
| End point title | Kaplan-Meier estimates for resolution of diarrhea |
| End point description: | |
| Resolution of Diarrhea (ROD) is defined as no more than 3 unformed bowel movements per day for at least two consecutive days for subjects on study treatment. The Kaplan-Meier estimates (KM estimates) for having an event (ROD) are reported for each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Day 10 | |

| End point values | Cadazolid | Vancomycin | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 301 | | |
| Units: KM estimate (% subjects with ROD) | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 | 51.0 (45.4 to 56.9) | 45.8 (40.4 to 51.6) | | |
| Day 2 | 64.5 (59.0 to 70.0) | 59.8 (54.3 to 65.4) | | |
| Day 3 | 69.7 (64.3 to 74.8) | 67.8 (62.5 to 73.0) | | |

| | | | | |
|--------|---------------------|---------------------|--|--|
| Day 4 | 73.8 (68.6 to 78.7) | 72.8 (67.6 to 77.7) | | |
| Day 5 | 77.9 (73.0 to 82.5) | 78.4 (73.6 to 82.9) | | |
| Day 6 | 77.9 (73.0 to 82.5) | 81.4 (76.8 to 85.6) | | |
| Day 7 | 79.7 (74.8 to 84.1) | 83.7 (79.3 to 87.6) | | |
| Day 8 | 81.0 (76.3 to 85.3) | 85.7 (81.5 to 89.4) | | |
| Day 9 | 81.0 (76.3 to 85.3) | 85.7 (81.5 to 89.4) | | |
| Day 10 | 81.0 (76.3 to 85.3) | 85.7 (81.5 to 89.4) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Main analysis |
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7794 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.24 |

Notes:

[5] - two-sided p-value (alpha 5%) based on log-rank test stratified by first occurrence / first recurrence and geographical region.

Secondary: Change from baseline to Day 3 in Clostridium difficile infection (CDI) daily symptoms Patient-Reported Outcome (CDI-DaySyms PRO) domain scores

| | |
|-----------------|--|
| End point title | Change from baseline to Day 3 in Clostridium difficile infection (CDI) daily symptoms Patient-Reported Outcome (CDI-DaySyms PRO) domain scores |
|-----------------|--|

End point description:

CDI-DaySyms PRO is a questionnaire assessing 10 symptoms relevant to subjects with CDAD and grouped into 3 domains: Diarrhea symptoms, Abdominal symptoms and Systemic/Other. The subjects rate the severity of each item as None, Mild, Moderate, Severe or Very severe, converted to numeric scores from 0 to 4, respectively. The daily domain score is calculated as the mean of the non-missing responses for that domain on that day. A negative value for change from baseline corresponds to an improvement in domain score. The three domains are evaluated in a hierarchical manner, starting with Diarrhea Symptoms, then Abdominal Symptoms, and finally Systemic/Other Symptoms. population used: All subjects from the mITT, excluding those who participated in the validation sub-study. No imputation of missing scores was performed prior to deriving response status. Subjects with missing values at baseline or at Day 3 were considered to be non-responders.

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

End point timeframe:

Baseline to End of Treatment (10 days after starting study drug) + 2 days

| End point values | Cadazolid | Vancomycin | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 232 | 245 | | |
| Units: Scores on a scale | | | | |
| number (confidence interval 95%) | | | | |
| Diarrhea symptoms | -1.242 (-1.40 to -1.09) | -1.199 (-1.35 to -1.05) | | |
| Abdominal symptoms | -0.669 (-0.79 to -0.54) | -0.693 (-0.82 to -0.57) | | |
| Other symptoms | -0.670 (-0.77 to -0.56) | -0.731 (-0.83 to -0.63) | | |

Statistical analyses

| Statistical analysis title | Comparison of the diarrhea domain scores |
|--|--|
| Statistical analysis description: ANOVA model for repeated measurements was fitted using all values from Day 1 (baseline) to Day 12. The Least Square Means of the treatments differences for the changes from baseline at Day 3 were obtained using estimate statements. | |
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 477 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6871 ^[6] |
| Method | ANOVA |
| Parameter estimate | Least square means difference |
| Point estimate | -0.044 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.17 |

Notes:

[6] - Two-sided 5% alpha level was used

| Statistical analysis title | Comparison of the abdominal symptoms domain scores |
|--|--|
| Statistical analysis description: ANOVA model for repeated measurements was fitted using all values from Day 1 (baseline) to Day 12. The Least Square Means of the treatments differences for the changes from baseline at Day 3 were obtained using estimate statements. | |
| Comparison groups | Cadazolid v Vancomycin |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 477 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7833 ^[7] |
| Method | ANOVA |
| Parameter estimate | Least Square Mean difference |
| Point estimate | 0.025 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.2 |

Notes:

[7] - Two-sided 5% alpha level was used

| | |
|-----------------------------------|--|
| Statistical analysis title | Comparison of the other symptoms domain scores |
|-----------------------------------|--|

Statistical analysis description:

ANOVA model for repeated measurements was fitted using all values from Day 1 (baseline) to Day 12. The Least Square Means of the treatments differences for the changes from baseline at Day 3 were obtained using estimate statements.

| | |
|---|------------------------------|
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 477 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4145 ^[8] |
| Method | ANOVA |
| Parameter estimate | Least Square Mean difference |
| Point estimate | 0.061 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.21 |

Notes:

[8] - Two-sided 5% alpha level was used

Other pre-specified: Investigator's assessment of clinical response (ICR) rate at Visit 4 in the modified intent-to-treat population

| | |
|-----------------|---|
| End point title | Investigator's assessment of clinical response (ICR) rate at Visit 4 in the modified intent-to-treat population |
|-----------------|---|

End point description:

ICR rate (%) is the percentage of subjects with clinical response assessed as cured according to the investigator's own judgement. Subjects with missing assessment are considered as not cured for the analysis. ICR rate is used as a supportive measure of the primary efficacy endpoint (CCR). Analyses are performed on two analysis sets. Results on the modified intent-to-treat set (mITT) are reported below.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to Day 12 on average (up to end-of-treatment + 2 to 4 days)

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 301 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 87.2 (82.9 to 90.6) | 88.4 (84.3 to 91.5) | | |

Statistical analyses

| Statistical analysis title | Exploratory analysis |
|---|----------------------------------|
| Comparison groups | Cadazolid v Vancomycin |
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.5 |
| upper limit | 4.2 |

Other pre-specified: Investigator's assessment of clinical response (ICR) rate at Visit 4 in the per-protocol population

| | |
|------------------------|--|
| End point title | Investigator's assessment of clinical response (ICR) rate at Visit 4 in the per-protocol population |
| End point description: | ICR rate (%) is the percentage of subjects with clinical response assessed as cured according to the investigator's own judgement. ICR rate (%) is the percentage of subjects with ICR assessed as cured. Subjects with missing assessment are considered as not cured for the analysis. ICR rate is used as a supportive measure of the primary efficacy endpoint (CCR). Analyses are performed on two analysis sets. Results on the per-protocol set (PPS) are reported below. |
| End point type | Other pre-specified |
| End point timeframe: | Up to Day 12 on average (up to end-of-treatment + 2 to 4 days) |

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 259 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 91.1 (86.9 to 94.0) | 92.7 (88.8 to 95.3) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Exploratory analysis |
| Comparison groups | Vancomycin v Cadazolid |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.5 |
| upper limit | 3.3 |

Other pre-specified: Investigator's assessment of sustained response rate (ISR rate) at Visit 5

| | |
|-----------------|--|
| End point title | Investigator's assessment of sustained response rate (ISR rate) at Visit 5 |
|-----------------|--|

End point description:

ISR rate (%) is the percentage of subjects assessed as Sustained Cure at Visit 5, according to the investigator's own judgement. Sustained Cure is defined for each subject having Clinical Cure and no recurrence. Subjects with missing assessment are considered as having 'Not Sustained Cure' for the analysis. ISR rate is used as a supportive measure of the secondary efficacy endpoint (SCR). Analyses are performed on the modified intent-to-treat set (mITT).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Between Day 38 and Day 42 on average (end-of-treatment + 28 to 32 days)

| | | | | |
|-----------------------------------|---------------------|---------------------|--|--|
| End point values | Cadazolid | Vancomycin | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 301 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 69.3 (63.8 to 74.3) | 60.5 (54.8 to 65.8) | | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Exploratory analysis |
| Comparison groups | Vancomycin v Cadazolid |

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 591 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | 8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 16.4 |

Other pre-specified: Sustained Cure Rate (SCR) in the per-protocol population

| | |
|--|--|
| End point title | Sustained Cure Rate (SCR) in the per-protocol population |
| End point description: | |
| Sustained Cure is defined for each subject having Clinical Cure and no recurrence. SCR is the percentage of subjects with Sustained Cure. The analyses performed on the modified intent-to- treat set (mITT) are repeated on the per-protocol set (PPS) for sensitivity. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Between Day 38 and Day 42 on average (end-of-treatment + 28-32 days) | |

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 259 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 67.6 (61.5 to 73.1) | 64.9 (58.9 to 70.4) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Sensitivity analysis |
| Comparison groups | Vancomycin v Cadazolid |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Difference between 2 proportions |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.5 |
| upper limit | 10.9 |

Other pre-specified: Recurrence rate

| | |
|-----------------|-----------------|
| End point title | Recurrence rate |
|-----------------|-----------------|

End point description:

Recurrence is defined as the occurrence of a new episode of diarrhea (> 3 unformed bowel movements on any day between end-of-treatment + 3 days and end-of-treatment + 30 days) Recurrence rates is the percentage of subjects assessed as having a recurrence out of subjects with Clinical Cure.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Between Day 13 and Day 40 on average (from end-of-treatment + 3 days and end-of-treatment + 30 days)

| End point values | Cadazolid | Vancomycin | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 235 | 258 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 15.7 (11.6 to 20.9) | 17.8 (13.6 to 23.0) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and frequent adverse events are reported from study treatment initiation up to Day 17 on average (i.e., 7 days after EOT or study withdrawal) and all-cause mortality up to Day 40 on average (i.e. 28 to 32 days after EOT on average)

Adverse event reporting additional description:

294 subjects who received at least one dose of cadazolid (cadazolid arm) and 307 subjects who received at least one dose of vancomycin (vancomycin arm) were included in the safety analysis. The median duration of treatment was 10 days in both arms.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Cadazolid |
|-----------------------|-----------|

Reporting group description:

Subjects who received oral cadazolid 250 mg twice daily (bid) for 10 days on average

| | |
|-----------------------|------------|
| Reporting group title | Vancomycin |
|-----------------------|------------|

Reporting group description:

Subjects who received oral vancomycin 125 mg 4 times per day (qid) for 10 days on average

| Serious adverse events | Cadazolid | Vancomycin | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 294 (11.90%) | 46 / 307 (14.98%) | |
| number of deaths (all causes) | 11 | 15 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer metastatic | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Immune system disorders | | | |
| Transplant rejection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 307 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia test positive | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Contrast media reaction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Porphyria acute | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Cholangitis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|-----------------|------------------|--|
| Bronchitis fungal | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 2 / 307 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 5 / 294 (1.70%) | 11 / 307 (3.58%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter sepsis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes simplex hepatitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 4 / 307 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia klebsiella | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 4 / 294 (1.36%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Transplant abscess | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 4 / 307 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 307 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 307 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cadazolid | Vancomycin | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 294 (15.99%) | 51 / 307 (16.61%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 294 (4.42%) | 18 / 307 (5.86%) | |
| occurrences (all) | 15 | 21 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 294 (5.10%) | 11 / 307 (3.58%) | |
| occurrences (all) | 20 | 12 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 16 / 294 (5.44%) | 11 / 307 (3.58%) | |
| occurrences (all) | 19 | 13 | |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 10 / 294 (3.40%) | 17 / 307 (5.54%) | |
| occurrences (all) | 11 | 17 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 December 2014 | Main reason for amendment: the main analysis of the primary endpoint (Clinical Cure) initially planned to be performed on the per-protocol population will be conducted on both the modified Intent-to-Treat and Per Protocol populations. Further changes include the addition of an emerging hypervirulent <i>Clostridium difficile</i> strain, the addition of endpoints related to susceptibility testing of <i>C. difficile</i> and vancomycin-resistant enterococci, and general clarifications of eligibility criteria and statistical analyses including a modification to the definition of recurrence for analyses of secondary variable sustained cure rate. |
| 22 October 2015 | Main reason: To remove the interim analysis originally planned after the randomization of 67% of the subjects. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported