



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
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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
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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
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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
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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
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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
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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)
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Subject analysis set type	Intention-to-treat
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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)
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Subject analysis set type	Per protocol
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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)
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Subject analysis set type	Safety analysis
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	Cadazolid
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Reporting group description:

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

Reporting group title	Vancomycin
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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 Clostridium difficile strain, the addition of endpoints related to susceptibility testing of C. difficile 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