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	2013-002528-17
Trial protocol	DE IT ES PL NL
Global end of trial date	24 March 2017

Results information

Result version number	v1 (current)
This version publication date	07 April 2018
First version publication date	07 April 2018

Trial information

Trial identification

Sponsor protocol code	AC-061A301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987895
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Global Scientific Information, 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	24 March 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 was non-inferior to oral vancomycin in subjects with Clostridium difficile-associated diarrhea (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	28 March 2014
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: 213
Country: Number of subjects enrolled	Canada: 173
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Romania: 102
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Peru: 1
Worldwide total number of subjects	632
EEA total number of subjects	234

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)	389
From 65 to 84 years	222
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

904 patients at 70 sites in 12 countries were screened, among whom 632 were enrolled in the IMPACT 1 trial at 64 sites located in North & South America, Europe and Australia.

Pre-assignment

Screening details:

Screening assessments were to be performed up to a maximum of 48 h, from the signature of the informed consent form to randomization

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 day 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 day of cadazolid + 30-day follow up)

Arm type	Active comparator

Investigational medicinal product name	Cadazolid-matching placebo
Investigational medicinal product code	
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, without active substance

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

Number of subjects in period 1	Cadazolid	Vancomycin
Started	306	326
Completed	276	296
Not completed	30	30
Adverse event, serious fatal	7	7
Consent withdrawn by subject	12	7
Physician decision	8	10
Lost to follow-up	3	5
randomized before giving IC	-	1

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 day 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 day of cadazolid + 30-day follow up)	

Reporting group values	Cadazolid	Vancomycin	Total
Number of subjects	306	326	632
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.6	55.6	
standard deviation	± 17.2	± 18.0	-
Gender categorical Units: Subjects			
Female	186	198	384
Male	120	128	248

Subject analysis sets	
Subject analysis set title	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	

Reporting group values	Intent-to-treat set (mITT)	Per protocol set (PPS)	Safety set (SS)
Number of subjects	620	570	626
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 56.5 ± 17.6	 ±	 ±
Gender categorical Units: Subjects			
Female	378		
Male	242		

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 day 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 day of cadazolid + 30-day follow up)

Subject analysis set title	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 (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 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	302	318		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	83.8 (79.2 to 87.5)	85.2 (80.9 to 88.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference between 2 proportions
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	4.3

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%. The 95%CI difference in proportion was estimated using the Wilson's score method.

Statistical analysis title	Statistical analysis 2

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	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference between 2 proportions
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	3.2

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%. The 95%CI difference in proportion was 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	282	288		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	87.6 (83.2 to 90.9)	91.7 (87.9 to 94.3)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference between 2 proportions
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	1

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%. The 95%CI difference in proportion was 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	302	318		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	65.6 (60.0 to 70.7)	62.3 (56.8 to 67.4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Cadazolid v Vancomycin
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Difference between 2 proportions
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	10.8

Notes:

[4] - Superiority of cadazolid versus vancomycin is demonstrated if the lower limit of the 95% confidence interval (CI) is above zero.
The 95%CI difference in proportion was 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	302	318		
Units: KM estimate (%)				
number (confidence interval 95%)				
Day 1	46.7 (41.2 to 52.5)	45.9 (40.6 to 51.6)		
Day 2	62.6 (57.2 to 68.0)	60.7 (55.4 to 66.1)		
Day 3	69.9 (64.6 to 74.9)	71.1 (66.0 to 76.0)		

Day 4	72.8 (67.7 to 77.7)	77.7 (73.0 to 82.1)		
Day 5	77.8 (73.0 to 82.3)	80.2 (75.6 to 84.4)		
Day 6	81.1 (76.5 to 85.3)	81.8 (77.3 to 85.8)		
Day 7	82.5 (78.0 to 86.5)	84.6 (80.4 to 88.3)		
Day 8	83.4 (79.0 to 87.4)	85.2 (81.1 to 88.9)		
Day 9	83.8 (79.4 to 87.7)	85.2 (81.1 to 88.9)		
Day 10	83.8 (79.4 to 87.7)	85.2 (81.1 to 88.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6016 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.14

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. A decrease in domain score indicates a better outcome.

End point type	Secondary

End point timeframe:

Day 3

End point values	Cadazolid	Vancomycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	260		
Units: LSM Estimates				
least squares mean (confidence interval 95%)				
Diarrhea symptoms	-1.233 (-1.37 to -1.09)	-1.235 (-1.37 to -1.10)		
Abdominal symptoms	-0.623 (-0.74 to -0.51)	-0.710 (-0.82 to -0.60)		
Other symptoms	-0.639 (-0.74 to -0.54)	-0.689 (-0.79 to -0.59)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Comparison of the diarrhea domain scores	
Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9814 [6]
Method	ANOVA
Parameter estimate	Least Square Mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Notes:

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

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Comparison of the abdominal symptoms domain scores	
Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2879 [7]
Method	ANOVA
Parameter estimate	Least Square Mean difference
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.25

Notes:

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

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Comparison of the systemic / other symptoms domain scores

Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488 [8]
Method	ANOVA
Parameter estimate	Least Square Mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.19

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	302	318		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	89.7 (85.8 to 92.7)	91.5 (87.9 to 94.1)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Exploratory analysis	
Comparison groups	Cadazolid v Vancomycin
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Difference between 2 proportions
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	2.9

Notes:

[9] - The 95%CI difference in proportion was estimated using the Wilson's score method.

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	282	288		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	92.2 (88.5 to 94.8)	94.1 (90.8 to 96.3)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Exploratory analysis	
Comparison groups	Cadazolid v Vancomycin

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Difference between 2 proportions
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	2.3

Notes:

[10] - The 95%CI difference in proportion was estimated using the Wilson's score method.

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	302	318		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	73.8 (68.6 to 78.5)	70.1 (64.9 to 74.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Exploratory analysis

Comparison groups	Vancomycin v Cadazolid

Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Difference between 2 proportions
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	10.7

Notes:

[11] - The 95%CI difference in proportion was estimated using the Wilson's score method.

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	282	288		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of participants	68.8 (63.2 to 73.9)	67.7 (62.1 to 72.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Sensitivity analysis

Comparison groups	Vancomycin v Cadazolid
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Difference between 2 proportions
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	8.7

Notes:

[12] - The 95%CI difference in proportion was estimated using the Wilson's score method.

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	253	271		
Units: percentage of participants				
number (confidence interval 95%)				
percentage of participants	15 (11.1 to 19.9)	21.4 (16.9 to 26.7)		

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)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Vancomycin

Reporting group description:

322 subjects received at least one dose of vancomycin and were included in the safety analysis. The median duration of treatment with vancomycin was 10 days.

Reporting group title	Cadazolid

Reporting group description:

304 subjects received at least one dose of cadazolid and were included in the safety analysis. The median duration of treatment with cadazolid was 10 days.

Serious adverse events	Vancomycin	Cadazolid	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 322 (8.07%)	19 / 304 (6.25%)	
number of deaths (all causes)	7	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic carcinoma of the bladder			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (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 chest syndrome			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary anastomosis complication			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrioventricular block second degree			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure congestive			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (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 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertransaminasaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile infection			
subjects affected / exposed	8 / 322 (2.48%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Perineal abscess			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 322 (0.62%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (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 pseudomonal			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (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			
Dehydration			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (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	Vancomycin	Cadazolid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 322 (15.22%)	33 / 304 (10.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 322 (7.76%)	14 / 304 (4.61%)	
occurrences (all)	28	17	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	22 / 322 (6.83%)	14 / 304 (4.61%)	
occurrences (all)	24	16	
Nausea			
subjects affected / exposed	24 / 322 (7.45%)	12 / 304 (3.95%)	
occurrences (all)	27	13	

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	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