

**Clinical trial results:****A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Assess the Safety and Efficacy of VP 20621 for Prevention of Recurrence of Clostridium difficile Infection (CDI) in Adults Previously Treated for CDI****Summary**

EudraCT number	2010-020484-20
Trial protocol	BE DE ES
Global end of trial date	11 June 2013

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	28 February 2015

Trial information**Trial identification**

Sponsor protocol code	20621-200
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01259726
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ViroPharma Incorporated
Sponsor organisation address	730 Stockton Drive, Exton, Pennsylvania, United States, 19341
Public contact	20621-200 Study Team, ViroPharma Incorporated, 1 610321 6215, VP20621-200@viropharma.com
Scientific contact	20621-200 Study Team, ViroPharma Incorporated, 1 610321 6215, VP20621-200@viropharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to: (1) evaluate the safety and tolerability of VP 20621 dosed orally for up to 14 days in adults previously treated for CDI; (2) characterize the frequency and duration of stool colonization with the VP 20621 strain of Clostridium (C.) difficile; (3) evaluate the efficacy of VP 20621 for prevention of recurrence of CDI; and (4) select a dose regimen of VP 20621 to be used in future studies.

Protection of trial subjects:

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	173
EEA total number of subjects	19

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)	106
From 65 to 84 years	59
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a total of 44 investigative sites [United states (US)=33, Canada=4, and Europe=7], and 3 of the 33 US sites did not enroll any subjects (each had 1 screen failure).

Pre-assignment

Screening details:

Of the 213 subjects formally screened to participate in this study, 40 subjects were screen failures. The most common reason for screen failure was violation of one or more inclusion/exclusion criteria in 29 subjects, followed by withdrawal of consent in 10 subjects, and death of 1 subject during screening period.

Pre-assignment period milestones

Number of subjects started	173
Intermediate milestone: Number of subjects	Treated: 168
Number of subjects completed	168

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Feeling poorly: 1
Reason: Number of subjects	Violation of exclusion criterion: 1
Reason: Number of subjects	Screen failures: 2

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to VP 20621 oral liquid once daily from Day 1 to 14.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to VP 20621 oral liquid once daily from Day 1 to 14.

Arm title	VP 20621 Low Dose and Placebo
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Arm description:

VP 20621 oral liquid containing 10^4 purified spores of non-toxigenic Clostridium difficile-strain M3 (NTCD-M3; the dormant form of a live organism) once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Arm type	Experimental
Investigational medicinal product name	VP 20621
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

VP 20621 oral liquid containing 10^4 purified spores of NTCD-M3 once daily from Day 1 to 7.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Arm title	VP 20621 High Dose and Placebo
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Arm description:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Arm type	Experimental
Investigational medicinal product name	VP 20621
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 7.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Arm title	VP 20621 High Dose
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Arm description:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 14.

Arm type	Experimental
Investigational medicinal product name	VP 20621
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 14.

Number of subjects in period 1 ^[1]	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo
	Started	43	41
Treated	40	37	41
Completed	38	37	39
Not completed	5	4	4
Consent withdrawn by subject	1	3	2
Physician decision	2	-	1
Death	1	-	-
Lost to follow-up	1	1	1

Number of subjects in period 1 ^[1]	VP 20621 High Dose
	Started
Treated	39
Completed	36
Not completed	5
Consent withdrawn by subject	1
Physician decision	1
Death	-
Lost to follow-up	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All enrolled subjects were not treated. Since baseline period consisted of only treated subjects, the worldwide number enrolled in the trial differs with number of subjects in baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to VP 20621 oral liquid once daily from Day 1 to 14.	
Reporting group title	VP 20621 Low Dose and Placebo
Reporting group description: VP 20621 oral liquid containing 10^4 purified spores of non-toxicogenic Clostridium difficile-strain M3 (NTCD-M3; the dormant form of a live organism) once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.	
Reporting group title	VP 20621 High Dose and Placebo
Reporting group description: VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.	
Reporting group title	VP 20621 High Dose
Reporting group description: VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 14.	

Reporting group values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo
Number of subjects	43	41	43
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	54.7 ± 19.19	58.2 ± 14.42	57.2 ± 18.46
Gender categorical Units: Subjects			
Female	26	26	24
Male	17	15	19

Reporting group values	VP 20621 High Dose	Total	
Number of subjects	41	168	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	60.6 ± 16.4	-	
Gender categorical Units: Subjects			
Female	28	104	
Male	13	64	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	Placebo matched to VP 20621 oral liquid once daily from Day 1 to 14.
Reporting group title	VP 20621 Low Dose and Placebo
Reporting group description:	VP 20621 oral liquid containing 10^4 purified spores of non-toxigenic Clostridium difficile-strain M3 (NTCD-M3; the dormant form of a live organism) once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.
Reporting group title	VP 20621 High Dose and Placebo
Reporting group description:	VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.
Reporting group title	VP 20621 High Dose
Reporting group description:	VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 14.
Subject analysis set title	Intent-to-Treat-Safety (ITT-S) population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	ITT-S population was defined as all randomized subjects who received at least 1 dose of study drug.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) ^[1]			
End point description:	An adverse event (AE) is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a study subject, regardless of causal relationship. TEAEs were defined as all AEs that start during the study drug treatment period (and up to 7 days after the last dose of the study drug) and were not seen at baseline, or were seen at baseline but increased in frequency and/or severity during the study drug treatment period (and up to 7 days after the last dose of study drug). SAE was any AE that results in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of an existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, other medically important events based upon appropriate medical judgement.			
End point type	Primary			
End point timeframe:	Baseline up to 7 days after the last dose of study drug (up to Week 3)			
Notes:	[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Statistical analysis was not planned for this endpoint.			

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[2]	41 ^[3]	43 ^[4]	41 ^[5]
Units: subjects				
Subjects with TEAEs	37	33	34	31
Subjects with treatment-emergent SAEs	3	1	1	2

Notes:

[2] - ITT-S population.

[3] - ITT-S population.

[4] - ITT-S population.

[5] - ITT-S population.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Positive Clostridium Difficile Stool Cultures Demonstrating Non-Toxigenic Clostridium Difficile-Strain M3

End point title	Number of Subjects With Positive Clostridium Difficile Stool Cultures Demonstrating Non-Toxigenic Clostridium Difficile-Strain M3
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End point description:

End point type	Primary
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End point timeframe:

After study drug administration period (14 days) through Week 6

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[6]	41 ^[7]	43 ^[8]	41 ^[9]
Units: subjects	4	26	31	29

Notes:

[6] - ITT-S population.

[7] - ITT-S population.

[8] - ITT-S population.

[9] - ITT-S population.

Statistical analyses

Statistical analysis title	Low dose+placebo versus placebo
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Statistical analysis description:

Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.

Comparison groups	VP 20621 Low Dose and Placebo v Placebo
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Number of subjects included in analysis	84
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	≤ 0.0001
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Method	Chi-squared
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Statistical analysis title	High dose+placebo versus placebo
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Statistical analysis description:

Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.

Comparison groups	Placebo v VP 20621 High Dose and Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Statistical analysis title

High dose versus placebo

Statistical analysis description:

Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.

Comparison groups	VP 20621 High Dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Number of Subjects With CDI Recurrence

End point title: Number of Subjects With CDI Recurrence

End point description:

CDI recurrence was defined as at least 1 event characterized by ALL of the following: ≥ 3 unformed (loose or watery) stools within 24 hours (data derived from Diarrhea case report form (CRF) page which was to be completed for any clinical event of diarrhea or loose/watery stool occurring between Day 1 and Week 6); a positive C. difficile stool assay, or pseudomembranes on endoscopy/surgery; and no other likely cause of the diarrhea in the opinion of the investigator.

End point type: Secondary

End point timeframe:

Baseline (Day 1) up to Week 6

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[10]	41 ^[11]	43 ^[12]	41 ^[13]
Units: subjects	13	6	2	6

Notes:

[10] - ITT-S population.

[11] - ITT-S population.

[12] - ITT-S population.

[13] - ITT-S population.

Statistical analyses

Statistical analysis title	Low dose+placebo versus placebo
Statistical analysis description:	
Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 Low Dose and Placebo v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Chi-squared

Statistical analysis title	High dose+placebo versus placebo
Statistical analysis description:	
Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 High Dose and Placebo v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Chi-squared

Statistical analysis title	High dose versus placebo
Statistical analysis description:	
Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 High Dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Chi-squared

Secondary: Number of Subjects With Use of Antibacterial Treatment for CDI

End point title	Number of Subjects With Use of Antibacterial Treatment for CDI
End point description:	
Any antibacterial medication used after Day 1 for which the investigator selected the indication "antibacterial for C. difficile infection".	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) up to Week 6	

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[14]	41 ^[15]	43 ^[16]	41 ^[17]
Units: subjects	14	6	4	7

Notes:

[14] - ITT-S population.

[15] - ITT-S population.

[16] - ITT-S population.

[17] - ITT-S population.

Statistical analyses

Statistical analysis title	Low dose+placebo versus placebo
Statistical analysis description: Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 Low Dose and Placebo v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Chi-squared

Statistical analysis title	High dose+placebo versus placebo
Statistical analysis description: Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 High Dose and Placebo v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Chi-squared

Statistical analysis title	High dose versus placebo
Statistical analysis description: Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.	
Comparison groups	VP 20621 High Dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Chi-squared

Secondary: Number of Subjects With Clinical Events of Diarrhea or Loose/Watery

Stools

End point title	Number of Subjects With Clinical Events of Diarrhea or Loose/Watery Stools
End point description:	Data were derived from all AEs starting on or after Day 1 for which a Diarrhea CRF page was completed.
End point type	Secondary
End point timeframe:	Baseline (Day 1) up to Week 6

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[18]	41 ^[19]	43 ^[20]	41 ^[21]
Units: subjects	33	23	25	23

Notes:

[18] - ITT-S population.

[19] - ITT-S population.

[20] - ITT-S population.

[21] - ITT-S population.

Statistical analyses

Statistical analysis title	Low dose+placebo versus placebo
Statistical analysis description:	Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.
Comparison groups	Placebo v VP 20621 Low Dose and Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Chi-squared

Statistical analysis title	High dose+placebo versus placebo
Statistical analysis description:	Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.
Comparison groups	VP 20621 High Dose and Placebo v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Chi-squared

Statistical analysis title	High dose versus placebo
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Statistical analysis description:

Treatment comparison with placebo using two-sided Chi-Square test at significance level $p=0.05$.

Comparison groups	VP 20621 High Dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Chi-squared

Secondary: Time to First CDI Recurrence

End point title	Time to First CDI Recurrence
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End point description:

CDI recurrence was defined as at least 1 event characterized by ALL of the following: ≥ 3 unformed (loose or watery) stools within 24 hours (data derived from Diarrhea CRF page which was to be completed for any clinical event of diarrhea or loose/watery stool occurring between Day 1 and Week 6); a positive C. difficile stool assay, or pseudomembranes on endoscopy/surgery; and no other likely cause of the diarrhea in the opinion of the investigator. Time of onset is from date of randomization to date of first CDI recurrence. Time to first CDI recurrence was assessed using Kaplan-Meier curve. '99999' in the below reported data indicates that median time to event was not evaluable due to small number of subjects (<50%) with CDI recurrence.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) up to Week 6

End point values	Placebo	VP 20621 Low Dose and Placebo	VP 20621 High Dose and Placebo	VP 20621 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43 ^[22]	41 ^[23]	43 ^[24]	41 ^[25]
Units: days				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

Notes:

[22] - ITT-S population.

[23] - ITT-S population.

[24] - ITT-S population.

[25] - ITT-S population.

Statistical analyses

Statistical analysis title	Low dose+placebo versus placebo
Comparison groups	Placebo v VP 20621 Low Dose and Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109
Method	Logrank

Statistical analysis title	High dose+placebo versus placebo
Comparison groups	VP 20621 High Dose and Placebo v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Logrank

Statistical analysis title	High dose versus placebo
Comparison groups	VP 20621 High Dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 26

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matched to VP 20621 oral liquid once daily from Day 1 to 14.

Reporting group title	VP20621 Low Dose and Placebo
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Reporting group description:

VP 20621 oral liquid containing 10^4 purified spores of NTCD-M3 once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Reporting group title	VP20621 High Dose and Placebo
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Reporting group description:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 7 followed by placebo matched to VP 20621 oral liquid once daily from Day 8 to 14.

Reporting group title	VP20621 High Dose
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Reporting group description:

VP 20621 oral liquid containing 10^7 purified spores of NTCD-M3 once daily from Day 1 to 14.

Serious adverse events	Placebo	VP20621 Low Dose and Placebo	VP20621 High Dose and Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 43 (18.60%)	5 / 41 (12.20%)	8 / 43 (18.60%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac chest pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	3 / 43 (6.98%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dependence			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	3 / 43 (6.98%)	1 / 41 (2.44%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VP20621 High Dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 41 (14.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lacunar infarction			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myoclonus			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Syncope			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac chest pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dependence			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	VP20621 Low Dose and Placebo	VP20621 High Dose and Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 43 (86.05%)	31 / 41 (75.61%)	34 / 43 (79.07%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 43 (4.65%)	6 / 41 (14.63%)	4 / 43 (9.30%)
occurrences (all)	3	11	6
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 43 (4.65%)	1 / 41 (2.44%)	2 / 43 (4.65%)
occurrences (all)	2	1	2
Abdominal pain			
subjects affected / exposed	16 / 43 (37.21%)	6 / 41 (14.63%)	9 / 43 (20.93%)
occurrences (all)	25	14	11
Abdominal pain upper			
subjects affected / exposed	1 / 43 (2.33%)	5 / 41 (12.20%)	2 / 43 (4.65%)
occurrences (all)	1	5	2
Constipation			
subjects affected / exposed	1 / 43 (2.33%)	2 / 41 (4.88%)	2 / 43 (4.65%)
occurrences (all)	1	2	2
Diarrhoea			
subjects affected / exposed	30 / 43 (69.77%)	21 / 41 (51.22%)	27 / 43 (62.79%)
occurrences (all)	117	69	84
Dyspepsia			

subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4	1 / 41 (2.44%) 1	2 / 43 (4.65%) 3
Flatulence subjects affected / exposed occurrences (all)	7 / 43 (16.28%) 7	9 / 41 (21.95%) 11	10 / 43 (23.26%) 10
Nausea subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 9	5 / 41 (12.20%) 7	4 / 43 (9.30%) 5
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	3 / 41 (7.32%) 3	1 / 43 (2.33%) 1
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	1 / 43 (2.33%) 1
Infections and infestations Clostridial infection subjects affected / exposed occurrences (all)	9 / 43 (20.93%) 13	2 / 41 (4.88%) 2	2 / 43 (4.65%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4	1 / 41 (2.44%) 1	1 / 43 (2.33%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 3	1 / 41 (2.44%) 1	1 / 43 (2.33%) 1

Non-serious adverse events	VP20621 High Dose		
Total subjects affected by non-serious adverse events subjects affected / exposed	34 / 41 (82.93%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Gastrointestinal disorders Abdominal distension			

subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 15		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 5		
Constipation subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	24 / 41 (58.54%) 82		
Dyspepsia subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 7		
Flatulence subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 9		
Nausea subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Infections and infestations Clostridial infection subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Nasopharyngitis			

subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2011	<ol style="list-style-type: none">1. The duration of the study was extended from 6 weeks to 6 months (Week 26)2. The removal of a separate follow-up study (Protocol 20621-900) for subjects who remained positive for <i>C. difficile</i> at Week 63. Duration of treatment for metronidazole or oral vancomycin for qualifying episode of CDI was extended from a maximum of 14 days to a maximum of 21 days4. Excluded subjects with acute febrile illness on Day 1 prior to the first dose, subjects with known immunodeficiency disorders and outpatient subjects with household contacts <2 years of age or who have an immunodeficiency disorder5. The first dose of study drug was to be administered under supervision of study personnel, and subjects were to remain at the study center for at least 30 minutes after the first dose6. The following information was to be recorded in the subject study diary: date and time of each study drug administration through Day 14, daily oral temperature measurement through Week 3; all AEs through Week 6, including severity assessment and any occurrence of specified gastrointestinal related events; date and time of any unformed (loose or watery) stools through Week 6; and medications through Week 67. The addition of oral temperature measurements, to be recorded at screening, Day 1, and each day through Week 38. A rapid urine pregnancy test performed at the study site on Day 1 prior to study drug was added for women of child-bearing potential9. All <i>C. difficile</i> isolates were to be tested for toxin A/B at a central lab, and any toxin-negative <i>C. difficile</i> was to be further genotyped10. All medications used within 1 week prior to study drug start and through Week 6 were to be recorded11. Permanent discontinuation of study drug if subject had Grade 3 or 4 neutropenia during the study drug administration period12. Clarified definitions and timeframe for several safety and efficacy endpoints, additional details to sample size assumptions, and added a Per Protocol population
29 March 2011	<ol style="list-style-type: none">1. Exclusion Criteria: "non-laparoscopic" gastrointestinal surgery and specification of Cluster of Differentiation 4 count, were removed2. New onset of medical conditions or changes in chronic disease was added to data to be recorded during follow-up Weeks 10-263. Megacolon was removed as a complication to be recorded for the qualifying episode of CDI
06 January 2012	<ol style="list-style-type: none">1. Inclusion Criteria: the time frame for the start of symptoms of the qualifying episode of CDI was changed from 21 days to 28 days, relative to randomization2. Clarified the required procedures if screening and randomization occurred on the same day3. A total of up to approximately 70 sites was increased from previously allowed 50 study sites4. Surgery removed as source for documentation of colonic pseudomembranes in inclusion criteria5. Excluded subjects with a known hypersensitivity to any ingredient in the study formulation6. Toxin A was removed from the testing of <i>C. difficile</i> isolates at the central lab since Toxin B is far more common7. The time period of events occurring between Day 1 and Week 6 was added, with regard to completion of the separate Diarrhea CRF page8. Temperature excursions between -20 to 25 degree Celsius were permitted for up to 72 hours9. The subgroup of gender was added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported