Clinical trial results:
A Phase 2b Parallel-Group, Double-Blind, Placebo-Controlled, Multicenter Study of SYN-004 Compared to Placebo for the Prevention of Clostridium difficile Associated Diarrhea in Patients with a Diagnosis of a Lower Respiratory Tract Infection

Summary

EudraCT number	2015-002346-32
Trial protocol	BG PL RO
Global end of trial date	10 November 2016

Results information

Result version number	v1 (current)
This version publication date	09 June 2018
First version publication date	09 June 2018

Trial information

Trial identification

Sponsor protocol code	SB-2-004-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02563106
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 73440

Notes:

Sponsors

Sponsor organisation name	Synthetic Biologics, Inc.
Sponsor organisation address	9605 Medical Center Dr. Suite 270, Rockville, United States, 20850
Public contact	Joe Sliman, Synthetic Biologics, Inc., 001 301-417-4364, jsliman@syntheticbiologics.com
Scientific contact	Joe Sliman, Synthetic Biologics, Inc., 001 301-417-4364, jsliman@syntheticbiologics.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	17 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2016
Global end of trial reached?	Yes
Global end of trial date	10 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness of treatment with SYN-004 for the prevention of Clostridium difficile (C. difficile) associated diarrhea (CDAD) in patients hospitalized for a lower respiratory tract infection receiving intravenous (IV) ceftriaxone alone or in combination with a macrolide.

To evaluate the safety and tolerability of SYN-004 in patients with a lower respiratory tract infection receiving IV ceftriaxone alone or in combination with a macrolide.

Protection of trial subjects:

No

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Romania: 102
Country: Number of subjects enrolled	Bulgaria: 101
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Serbia: 139
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	413
EEA total number of subjects	265

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	145
From 65 to 84 years	249
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Date First Subject Enrolled 16 NOV 2015
Date Last Subject Completed 10 NOV 2016

Pre-assignment

Screening details:

A total of 433 subjects were screened for this study, 413 were found to be eligible and were enrolled, and 412 of the enrolled subjects received study drug. Most subjects were enrolled in Europe: 139 subjects in Serbia, 102 in Romania, 101 in Bulgaria, 42 in Poland, and 20 in Hungary. The US enrolled 7 and Canada enrolled 2.

Pre-assignment period milestones

Number of subjects started	433[1]
Number of subjects completed	412

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion criteria not met: 10
Reason: Number of subjects	Exclusion criteria met: 6
Reason: Number of subjects	vendor issue: 1
Reason: Number of subjects	Inc and Exc criteria not met/met: 1
Reason: Number of subjects	Drug didnt arrive in time for dosing: 1
Reason: Number of subjects	IV ceftriaxone started greater than 24H: 1
Reason: Number of subjects	Subject randomized, but not dosed: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There was 1 subject that was randomized but did not dose,there fore they did pass the screening/rand period but did not receive study drug.

Period 1

Period 1 title	Treatment Period 1, 2 and Follow-Up (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:

At the start of Treatment Period 1 and during Treatment Period 2, eligible subjects were randomly assigned via an interactive voice/web response system to either SYN-004 or placebo. SYN-004 and placebo were prepared in identical capsules to ensure blinding. All Investigators, site staff, sponsor & vendor employees involved in the study were blinded to treatment until after database lock. The Follow-up Period lasted for 6 weeks and was used to collect safety data.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo
Arm description: Matching Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Matching placebo given 4 times a day	
Arm title	SYN-004
Arm description: 150 mg SYN-004	
Arm type	Experimental
Investigational medicinal product name	SYN-004
Investigational medicinal product code	
Other name	ribaxamase
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 150 mg in a delayed release capsule 4 times a day	

Number of subjects in period 1[2]	Placebo	SYN-004
Started	206	206
Completed	178	172
Not completed	28	34
Adverse event, serious fatal	5	11
Physician decision	1	3
Consent withdrawn by subject	7	7
Non-permitted concurrent therapy	2	1
Adverse event, non-fatal	10	6
Other	1	2
Lost to follow-up	2	3
Protocol deviation	-	1

Notes:

[2] - 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: There was 1 subject that was randomized but did not dose,there fore they did pass the screening/rand period but did not receive study drug.

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1, 2 and Follow-Up

Reporting group description: -

Reporting group values	Treatment Period 1, 2 and Follow-Up	Total	
Number of subjects	412	412	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	145	145	
From 65-84 years	248	248	
85 years and over	19	19	
Age continuous Units: years			
arithmetic mean	69.2		
standard deviation	± 9.37	-	
Gender categorical Units: Subjects			
Female	153	153	
Male	259	259	

Subject analysis sets

Subject analysis set title	SYN-004
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) analysis set included randomized subjects who received at least 1 dose of study drug.

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) analysis set included randomized subjects who received at least 1 dose of study drug.

Reporting group values	SYN-004	Placebo	
Number of subjects	206	206	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	74	71	
From 65-84 years	124	124	
85 years and over	8	11	
Age continuous			
Units: years			
arithmetic mean	68.8	69.7	
standard deviation	± 9.4	± 9.4	
Gender categorical			
Units: Subjects			
Female	73	80	
Male	133	126	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching Placebo	
Reporting group title	SYN-004
Reporting group description:	
150 mg SYN-004	
Subject analysis set title	SYN-004
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent-to-Treat (mITT) analysis set included randomized subjects who received at least 1 dose of study drug.	

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent-to-Treat (mITT) analysis set included randomized subjects who received at least 1 dose of study drug.	

Primary: Percentage of Patients With Clostridium difficile infection at 4-weeks of follow-up

End point title	Percentage of Patients With Clostridium difficile infection at 4-weeks of follow-up
End point description:	
Percentage of subjects with CDI, based on the protocol definition of CDI (defined as 3 or more unformed stools per 24 hour period and a stool sample being positive for C. difficile toxin A and/or B [or their respective genes, tcdA and/or tcdB], based on the clinical site local laboratory results) from Day 1 to the 4-week Follow-up Visit in the SYN-004 treatment group compared to the placebo group, imputing early termination without CDI as not being treatment failures	
End point type	Primary
End point timeframe:	
Day 1 to the 4 week Follow-up Visit.	

End point values	Placebo	SYN-004		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	206		
Units: count of participants	7	2		

Statistical analyses

Statistical analysis title	Comparison of CDI rates between treatment groups
Statistical analysis description:	
The Modified Intent-to-Treat (mITT) analysis set included randomized subjects who received at least 1 dose of study drug. Number of subjects with CDI, imputing early termination without CDI as not being treatment failures.	

Comparison groups	Placebo v SYN-004
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.1 [2]
Method	one-sided z-test
Parameter estimate	Relative Risk Reduction (%)
Point estimate	71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.9
upper limit	94
Variability estimate	Standard error of the mean

Notes:

[1] - The analysis of the primary endpoint was based on the mITT analysis set. The P-value was based on a pre-specified one-sided z-test for the comparison of the treatment difference between the SYN-004 group and the Placebo group.

[2] - Study was designed to provide 80% power to detect treatment effect with one-sided alpha = 0.05 on the primary endpoint. Based on the pre-specified z-test the one-sided P=0.045.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 weeks

Adverse event reporting additional description:

Note: The frequency threshold of 1% for non-serious adverse events is reported as the Number of subjects with Adverse Events (AEs) (excluding Serious Adverse Events (SAEs)) in each group, based on number of subjects with AEs >1% in the SYN-004 group and the corresponding AE categories for the Placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching Placebo

Reporting group title	SYN-004

Reporting group description:

150 mg SYN-004

Serious adverse events	Placebo	SYN-004	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 206 (10.19%)	33 / 206 (16.02%)	
number of deaths (all causes)	5	11	
number of deaths resulting from adverse events	5	11	
Investigations			
International normalised ratio abnormal			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia recurrent			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm			

subjects affected / exposed	1 / 206 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	1 / 206 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 206 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 206 (0.97%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (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 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	2 / 206 (0.97%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
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	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (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			
Syncope			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
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			

Anemia of Chronic Disease			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron Deficiency Anemia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 206 (0.97%)	4 / 206 (1.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 206 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
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	3 / 206 (1.46%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 206 (1.94%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 206 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 206 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 206 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 206 (2.43%)	4 / 206 (1.94%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pseudomembranous colitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	
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: 1 %

Non-serious adverse events	Placebo	SYN-004	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 206 (22.33%)	42 / 206 (20.39%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 206 (4.85%)	7 / 206 (3.40%)	
occurrences (all)	13	7	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 206 (0.97%)	3 / 206 (1.46%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 206 (2.91%)	5 / 206 (2.43%)	
occurrences (all)	7	5	
Insomnia			
subjects affected / exposed	9 / 206 (4.37%)	4 / 206 (1.94%)	
occurrences (all)	9	4	
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	6 / 206 (2.91%)	7 / 206 (3.40%)	
occurrences (all)	7	10	
Diarrhoea			
subjects affected / exposed	11 / 206 (5.34%)	9 / 206 (4.37%)	
occurrences (all)	11	9	
Nausea			
subjects affected / exposed	3 / 206 (1.46%)	5 / 206 (2.43%)	
occurrences (all)	3	5	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 206 (0.97%)	3 / 206 (1.46%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 206 (1.94%)	4 / 206 (1.94%)	
occurrences (all)	5	4	
Pleural effusion			
subjects affected / exposed	1 / 206 (0.49%)	3 / 206 (1.46%)	
occurrences (all)	1	3	
Pneumonia			
subjects affected / exposed	1 / 206 (0.49%)	3 / 206 (1.46%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 206 (0.49%)	3 / 206 (1.46%)	
occurrences (all)	1	3	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	3 / 206 (1.46%)	3 / 206 (1.46%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2016	The timing of the interim analysis was changed to occur when 80% of planned subjects have either completed the 4-week Follow-up Visit or early terminated the study before the 4-week Follow-up Visit. Previously the protocol indicated the interim analysis would occur when either 30% of the planned subjects completed the 4-week Follow-up Visit or early terminated the study and 10 cases of CDAD were identified or 50% of the subjects completed the 4-week Follow-up Visit or early terminated the study. Three additional secondary efficacy endpoints were added to the protocol to assist in the final analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A safety assessment conducted by an independent third party to evaluate SAEs and fatal events confirmed that they were related to the subjects' underlying health, medical history, and comorbidities and not to study drug administration.

Notes: