Clinical trial results:
An Open-Label, Dose-Finding Study of Vedolizumab IV for Treatment of Steroid-Refractory Acute Intestinal Graft-Versus-Host Disease (GvHD) in Patients who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

Summary

EudraCT number	2016-002985-30
Trial protocol	SE FR BE
Global end of trial date	09 May 2018

Results information

Result version number	v1 (current)
This version publication date	22 May 2019
First version publication date	22 May 2019

Trial information

Trial identification

Sponsor protocol code	Vedolizumab-2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993783
WHO universal trial number (UTN)	U1111-1185-6832

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Medical Director, Takeda, +1 8778253327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda, +1 8778253327, clinicaltrialregistry@tpna.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	09 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to describe the initial activity, tolerability, and safety and to identify a recommended dose and regimen of vedolizumab IV administered for treatment of steroid-refractory acute intestinal GvHD in participants who have undergone allo-HSCT.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2017
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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	17
EEA total number of subjects	9

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)	13
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 11 investigative sites in the United States, France, Belgium and Norway from 28 April 2017 to 09 May 2018.

Pre-assignment

Screening details:

Participants with steroid-refractory acute intestinal graft-versus-host disease (GvHD) who had undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT) were enrolled to receive 300 mg or 600 mg vedolizumab.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Vedolizumab 300 mg

Arm description:

Vedolizumab 300 mg, intravenous (IV) infusion, once on Days 1, 15, 43, 71 and 99.

Arm type	Experimental
Investigational medicinal product name	Vedolizumab IV
Investigational medicinal product code	MLN0002
Other name	Entyvio™
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab 300 mg, infusion, intravenously once on Days 1, 15, 43, 71 and 99

Arm title	Vedolizumab 600 mg

Arm description:

Vedolizumab 600 mg, IV infusion, once on Days 1, 15, 43, 71 and 99.

Arm type	Experimental
Investigational medicinal product name	Vedolizumab IV
Investigational medicinal product code	MLN0002
Other name	Entyvio™
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab 600 mg, infusion, intravenously once on Days 1, 15, 43, 71 and 99

Number of subjects in period 1	Vedolizumab 300 mg	Vedolizumab 600 mg
Started	8	9
Completed	2	0
Not completed	6	9
Reason not Specified	6	9

Baseline characteristics

Reporting groups	
Reporting group title	Vedolizumab 300 mg
Reporting group description:	
Vedolizumab 300 mg, intravenous (IV) infusion, once on Days 1, 15, 43, 71 and 99.	
Reporting group title	Vedolizumab 600 mg
Reporting group description:	
Vedolizumab 600 mg, IV infusion, once on Days 1, 15, 43, 71 and 99.	

Reporting group values	Vedolizumab 300 mg	Vedolizumab 600 mg	Total
Number of subjects	8	9	17
Age categorical Units: Subjects			
Adults (18-64 years)	7	6	13
From 65-84 years	1	3	4
Age Continuous Units: years			
arithmetic mean	54.1	59.0	
standard deviation	± 10.45	± 10.87	-
Sex: Female, Male Units: Subjects			
Female	6	4	10
Male	2	5	7
Baseline Eastern Cooperative Oncology Group (ECOG) Status			
ECOG assessed participant's performance status on a 6 point scale: 0=Normal activity (fully active, able to carry on all predisease performance without restriction); 1=Symptoms but ambulatory (restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature); 2=In bed <50% of the time (ambulatory and capable of all self-care, but unable to carry out any work activities); 3=In bed >50% of the time (capable of only limited self-care); 4=100% bedridden (completely disabled, cannot carry on any selfcare, totally confined to bed or chair) 5=Dead.			
Units: Subjects			
Score = 0	2	0	2
Score = 1	3	2	5
Score = 2	1	4	5
Score = 3	2	3	5
Region of Enrollment Units: Subjects			
Belgium|	2	2	4
France|	3	1	4
Norway|	0	1	1
United States|	3	5	8
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	6	9	15
Not Reported	2	0	2
Race/Ethnicity, Customized Units: Subjects			
White	7	9	16

Not Reported	1	0	1

Height			
Units: cm			
arithmetic mean	170.3	169.8	
standard deviation	± 12.08	± 7.87	-
Weight			
Units: kg			
arithmetic mean	76.40	74.01	
standard deviation	± 16.900	± 22.255	-

End points

End points reporting groups

Reporting group title	Vedolizumab 300 mg
Reporting group description:	
Vedolizumab 300 mg, intravenous (IV) infusion, once on Days 1, 15, 43, 71 and 99.	
Reporting group title	Vedolizumab 600 mg
Reporting group description:	
Vedolizumab 600 mg, IV infusion, once on Days 1, 15, 43, 71 and 99.	

Primary: Percentage of Participants with Overall Response (Partial Response [PR]+Very Good Partial Response [VGPR]+Complete Response [CR]) at Day 28

End point title	Percentage of Participants with Overall Response (Partial Response [PR]+Very Good Partial Response [VGPR]+Complete Response [CR]) at Day 28[1]

End point description:

CR is defined as the resolution of all signs and symptoms of acute graft-versus-host-disease (GvHD). VGPR is defined as resolution of the signs and symptoms of the GvHD: 1) Skin: no rash, or residual erythematous rash involving <25% of the body surface, without bullae (excluding residual faint erythema and hyperpigmentation). 2) Liver: total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment. 3) Gut: a) participant tolerates food or enteral feeding; b) predominantly formed stools; c) no overt gastrointestinal bleeding or abdominal cramping; d) no more than occasional nausea or vomiting. PR is defined as improvement of 1 GvHD stage in 1 or more organs without progression in any organ. Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Primary

End point timeframe:

Day 28

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	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (confidence interval 95%)	50.0 (15.7 to 84.3)	22.2 (2.8 to 60.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Experienced Serious Adverse Events (SAEs) Through Day 28

End point title	Number of Participants who Experienced Serious Adverse Events (SAEs) Through Day 28[2]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An SAE is defined as an untoward medical occurrence, significant hazard, contraindication, side effect or precaution that at any dose: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. Safety analysis set (SAS) included all participants who received any amount of the study drug.

End point type	Primary

End point timeframe:

From first dose up to Day 28

Notes:

[2] - 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	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Died in the Absence of Primary Malignancy Relapse After allo-HSCT at Month 6

End point title	Percentage of Participants who Died in the Absence of Primary Malignancy Relapse After allo-HSCT at Month 6

End point description:

Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (confidence interval 95%)	50.0 (15.7 to 84.3)	88.9 (68.4 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Acute GvHD Complete Response (CR) at Day 28

End point title	Percentage of Participants with Acute GvHD Complete Response (CR) at Day 28

End point description:

CR is defined as the resolution of all signs and symptoms of acute GvHD. Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Day 28

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (confidence interval 95%)	12.5 (0.3 to 52.7)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Intestinal Overall Response at Day 28

End point title	Percentage of Participants with Intestinal Overall Response at Day 28

End point description:

Symptoms of acute intestinal GvHD were measured using the BMT CTN-modified International Bone Marrow Transplant Registry Database (IBMTR) index. Intestinal overall response is either CR, VGPR or PR for intestine only. CR is defined as the resolution of all signs and symptoms of GvHD. VGPR is defined as resolution of the majority of signs and symptoms of intestinal GvHD: a) participant tolerates food or enteral feeding; b) predominantly formed stools; c) no overt gastrointestinal bleeding or abdominal cramping; d) no more than occasional nausea or vomiting. PR is defined as improvement of intestinal GvHD by at least 1 stage. Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Day 28

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (confidence interval 95%)	62.5 (24.5 to 91.5)	33.3 (7.5 to 70.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Percentage of Participants Achieving Survival at Months 6 and 12

End point title	Kaplan-Meier Estimate of Percentage of Participants Achieving Survival at Months 6 and 12

End point description:

The Kaplan-Meier estimate reports the percentage of participants surviving at Months 6 and 12. 9999 = Data not available (NA), due to a low number of participants with events. Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Months 6 and 12

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (confidence interval 95%)				
Month 6|	0.50 (0.15 to 0.77)	0.11 (0.01 to 0.39)		
Month 12|	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive Without GvHD or Primary Malignancy Relapse at Months 6 and 12

End point title	Percentage of Participants Alive Without GvHD or Primary Malignancy Relapse at Months 6 and 12

End point description:

Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Months 6 and 12

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percentage of participants				
number (not applicable)				
Month 6|	37.5	0		
Month 12|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of Steroids Administered

End point title	Total Dose of Steroids Administered

End point description:

Total Steroids administered in mg/kg/day of methylprednisolone or equivalent. Efficacy analysis set included all participants from the safety set who had baseline efficacy assessment and at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Months 6 and 12

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Month 6|	0.862 (± 0.6397)	0.876 (± 0.4796)		
Month 12|	0.829 (± 0.6611)	0.876 (± 0.4798)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs)

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. SAS included all participants who received any amount of the study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug to 18 weeks after last dose (Up to Week 32)

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants	8	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experienced Serious Adverse Events (SAEs) Through Week 32

End point title	Number of Participants who Experienced Serious Adverse Events (SAEs) Through Week 32

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An SAE is defined as an untoward medical occurrence, significant hazard, contraindication, side effect or precaution that at any dose: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. SAS included all participants who received any amount of the study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug to 18 weeks after last dose (Up to Week 32)

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants	6	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Markedly Abnormal Laboratory Parameters Values

End point title	Number of Participants with Markedly Abnormal Laboratory Parameters Values

End point description:

Clinical laboratory parameters included tests for chemistry, hematology, urinalysis. Markedly abnormal values during treatment period were:alanine aminotransferase (ALT)>3.0 U/L*upper limit of normal(ULN),albumin<25 g/L*lower limit of normal(LLN),alkaline phosphatase>3.0 U/L*ULN,aspartate aminotransferase >3.0 U/L*ULN,bilirubin>2 umol/L*ULN,blood urea nitrogen(BUN) >10.7 mmol/L,calcium <1.75 mmol/L, >2.88 mmol/L,chloride<75 mmol/L, >126 mmol/L,creatinine >177umol/L,gamma glutamyl transferase (GGT) >3 U/L*ULN,glucose <2.8 mmol/L, >19.4 mmol/L,phosphate <0.52 mmol/L, >2.10 mmol/L,potassium<3 mmol/L, >6 mmol/L,sodium <130 mmol/L, >150 mmol/L,basophils >3(10^9/L)*ULN,eosinophils >2(10^9/L)*ULN,hematocrit (%) <0.8*LLN, >1.2*ULN,hemoglobin <0.8 g/L*LLN, >1.2 g/L*ULN,leukocytes <0.5 (10^9/L)*LLN, >1.5 (10^9/L)*ULN,lymphocytes <0.5 (10^9/L)*LLN, >1.5(10^9/L)*ULN,monocytes >2 (10^9/L)*ULN,neutrophils <0.5(10^9/L)*LLN, >1.5 (10^9/L)*ULN,platelets <75(10^9/L),

End point type	Secondary

End point timeframe:

From Baseline up to last dose of study drug (Day 99)

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants				
ALT >3.0 U/L*ULN|	4	0		
Albumin <25 g/L*LLN|	4	8		
Alkaline phosphatase >3.0 U/L*ULN|	1	0		
Aspartate aminotransferase >3.0 U/L*ULN|	1	0		
Bilirubin >2 umol/L*ULN|	1	2		
BUN >10.7 mmol/L|	3	6		
Calcium <1.75 mmol/L|	0	3		
Calcium >2.88 mmol/L|	0	0		
Chloride <75 mmol/L|	0	0		
Chloride >126 mmol/L|	0	0		
Creatinine >177umol/L|	0	1		
GGT >3 U/L*ULN|	5	2		
Glucose <2.8 mmol/L|	0	0		
Glucose >19.4 mmol/L|	1	0		
Phosphate <0.52 mmol/L|	0	0		
Phosphate >2.10 mmol/L|	0	1		
Potassium <3 mmol/L|	1	0		
Potassium >6 mmol/L|	0	0		
Sodium <130 mmol/L|	0	0		
Sodium >150 mmol/L|	0	0		
Basophils >3(10^9/L)*ULN|	0	0		
Eosinophils >2(10^9/L)*ULN|	0	0		
Hematocrit (%) <0.8*LLN|	7	8		

Hematocrit (%) >1.2*ULN|	0	0		
Hemoglobin <0.8 g/L*LLN|	7	8		
Hemoglobin >1.2 g/L*ULN|	0	0		
Leukocytes <0.5 (10^9/L)*LLN|	3	7		
Leukocytes >1.5 (10^9/L)*ULN|	1	0		
Lymphocytes <0.5 (10^9/L)*LLN|	7	9		
Lymphocytes >1.5(10^9/L)*ULN|	0	0		
Monocytes >2 (10^9/L)*ULN|	0	1		
Neutrophils <0.5(10^9/L)*LLN|	0	3		
Neutrophils >1.5 (10^9/L)*ULN|	1	1		
Platelets <75(10^9/L)|	8	9		
Platelets >600(10^9/L)|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Markedly Abnormal Vital Signs

End point title	Number of Participants with Markedly Abnormal Vital Signs

End point description:

Vital signs included heart rate, respiratory rate, systolic and diastolic blood pressure, temperature and weight. The vital sign values outside the range: systolic blood pressure (SBP) <85 mmHg and change from Baseline (BL) <=-20 mmHg, >180 mmHg and change from Baseline >=20 mmHg,diastolic blood pressure (DBP) <50 mmHg and change from Baseline <=-15 mmHg, >110 mmHg and change from Baseline >=15 mmHg, heart rate <50 beats per minute (bpm),>120 beats per minute, temperature <35.6 Degree C, >37.7 Degree C and weight change from Baseline <=-7 % and weight change from Baseline >=7 % assessed during treatment period were considered markedly abnormal. SAS included all participants who received any amount of the study drug.

End point type	Secondary

End point timeframe:

From Baseline up to last dose of study drug (Day 99)

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants				
SBP <85 mmHg and change from BL <=-20 mmHg|	0	0		
SBP >180 mmHg and change from BL >=20 mmHg|	1	0		
DBP <50 mmHg and change from BL<=-15 mmHg|	0	0		
DBP >110 mmHg and change from BL>=15 mmHg|	0	0		
Heart Rate <50 bpm|	0	0		
Heart Rate >120 bpm|	0	1		
Temperature <35.6 Degree C|	1	3		
Temperature >37.7 Degree C|	0	0		
Weight change from BL <=-7 %|	4	2		

Weight change from BL >=7 %|	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough: Trough Serum Concentrations of Vedolizumab

End point title	Ctrough: Trough Serum Concentrations of Vedolizumab

End point description:

Pharmacokinetic (PK) set included all participants from the safety set with at least 1 post dose PK sample collected.

End point type	Secondary

End point timeframe:

Day 99 (pre-dose)

End point values	Vedolizumab 300 mg	Vedolizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: ug/mL				
arithmetic mean (standard deviation)	40.2 (± 37.2)	12.3 (± 5.49)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 18 weeks after the last dose of study drug (Up to approximately 32 weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Vedolizumab 300 mg

Reporting group description:

Vedolizumab 300 mg, IV infusion, once on Days 1, 15, 43, 71 and 99.

Reporting group title	Vedolizumab 600 mg

Reporting group description:

Vedolizumab 600 mg, IV infusion, once on Days 1, 15, 43, 71 and 99.

Serious adverse events	Vedolizumab 300 mg	Vedolizumab 600 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	9 / 9 (100.00%)	
number of deaths (all causes)	4	9	
number of deaths resulting from adverse events	2	6	
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
Graft versus host disease			

subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Acute graft versus host disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in intestine			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in liver			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations			
Peritonitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Citrobacter sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Escherichia infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia necrotising			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vedolizumab 300 mg	Vedolizumab 600 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Anogenital warts			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	2	4	
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Jugular vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Venoocclusive disease			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 8 (37.50%)	3 / 9 (33.33%)	
occurrences (all)	3	6	
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Generalised oedema			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Hypogammaglobulinaemia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Graft versus host disease in skin			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Acute graft versus host disease in intestine			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Oropharyngeal pain			

subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	3	
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Respiratory failure			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Aspiration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Atelectasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hiccups			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Increased bronchial secretion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	
occurrences (all)	5	5	
Platelet count decreased			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	8	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	6	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Blood urea increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
BK polyomavirus test positive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood beta-D-glucan increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood creatine increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood pressure decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Cytomegalovirus test positive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	5	
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Laceration			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	
occurrences (all)	1	3	
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Ageusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Clonus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Embolic stroke			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Head titubation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 8 (50.00%)	3 / 9 (33.33%)	
occurrences (all)	6	4	
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	
occurrences (all)	1	5	
Thrombocytopenia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Aplasia pure red cell			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Dry eye			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eye pruritus			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	3 / 8 (37.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	

Gingival pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Haemorrhoids			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ileus paralytic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oral mucosa haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tongue discolouration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pain of skin			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Alopecia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Angioedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lichen planus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Onychoclasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	
occurrences (all)	2	3	
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	

Enterococcal infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
BK virus infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Klebsiella infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Staphylococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Aspergillus infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Clostridium difficile infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Clostridial infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Corona virus infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Enterobacter infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Escherichia infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Mastoiditis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pseudomonas infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Urosepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 8 (37.50%)	5 / 9 (55.56%)	
occurrences (all)	9	7	
Hyperglycaemia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 9 (22.22%)	
occurrences (all)	3	2	
Hypoalbuminaemia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 9 (33.33%)	
occurrences (all)	2	4	
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	
occurrences (all)	1	4	
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	5	
Hypermagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Acidosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Electrolyte imbalance			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Fluid imbalance			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2017	The following changes were made as per amendment 2 – • Clarified inclusion/exclusion criteria. • Clarify efficacy analyses. • Modified conduct of the interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported