



Clinical trial results:

A Randomized Double-Blind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE)

Summary

EudraCT number	2015-000852-12
Trial protocol	BE GB NL ES FR
Global end of trial date	14 November 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	Vedolizumab-4003
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02630966
WHO universal trial number (UTN)	U1111-1174-2252

Notes:

Sponsors

Sponsor organisation name	Takeda Takeda Development Centre Europe, Ltd.
Sponsor organisation address	61 Aldwych, WC2B 4AE, London, United Kingdom,
Public contact	Medical Director, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda, +1 877-825-3327, 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	14 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the percentage of participants with perianal fistula healing at Week 30 in 2 different dose regimens of vedolizumab intravenous (IV) 300 milligram (mg) in participants with fistulizing Crohn's disease (CD).

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	10 August 2016
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	Canada: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	34
EEA total number of subjects	28

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)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 13 investigative sites in Canada, France, Italy, the Netherlands, Spain, the United Kingdom, and the United States from 10 August 2016 to 14 November 2018.

Pre-assignment

Screening details:

Participants with a diagnosis of moderately to severely active Crohn's disease were randomized in a 1:1 ratio to receive vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 14, 22 and a vedolizumab placebo-matching IV dose at Week 10 or vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 10, 14, and 22.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Vedolizumab IV 300 mg + Placebo

Arm description:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 14, and 22, and vedolizumab placebo-matching, IV infusion once, at Week 10 to maintain the blind.

Arm type	Experimental
Investigational medicinal product name	Vedolizumab IV infusion
Investigational medicinal product code	
Other name	Entyvio MLN0002 Kynteles
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 14, and 22.

Investigational medicinal product name	Vedolizumab placebo-matching IV infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab placebo-matching, IV infusion once, at Week 10 to maintain the blind.

Arm title	Group 2: Vedolizumab 300 mg
------------------	-----------------------------

Arm description:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 10, 14, and 22.

Arm type	Experimental
Investigational medicinal product name	Vedolizumab IV Infusion
Investigational medicinal product code	
Other name	Entyvio MLN0002 Kynteles
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 10, 14, and 22.

Number of subjects in period 1	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg
Started	16	18
Completed	14	10
Not completed	2	8
Adverse event, non-fatal	1	3
Voluntary Withdrawal	-	2
Significant Protocol Deviation	1	1
Lack of efficacy	-	2

Baseline characteristics

Reporting groups

Reporting group title	Group 1: Vedolizumab IV 300 mg + Placebo
Reporting group description: Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 14, and 22, and vedolizumab placebo-matching, IV infusion once, at Week 10 to maintain the blind.	
Reporting group title	Group 2: Vedolizumab 300 mg
Reporting group description: Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 10, 14, and 22.	

Reporting group values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg	Total
Number of subjects	16	18	34
Age categorical Units: Subjects			
From 18-64 years	16	18	34
Age Continuous Units: years			
arithmetic mean	35.1	35.1	
standard deviation	± 10.35	± 10.67	-
Sex: Female, Male Units: Subjects			
Female	6	7	13
Male	10	11	21
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2	3	5
Unknown or Not Reported	14	15	29
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	12	15	27
More than one race	0	0	0
Unknown or Not Reported	2	3	5
Smoking Classification Units: Subjects			
Never-smoker	7	8	15
Current smoker	7	4	11
Ex-smoker	2	6	8
Region of Enrollment Units: Subjects			
Canada	1	0	1
France	2	3	5

Italy	5	6	11
Netherlands	2	3	5
Spain	3	2	5
United Kingdom	1	1	2
United States	2	3	5
Height			
Units: centimeter (cm)			
arithmetic mean	170.1	176.4	
standard deviation	± 6.35	± 10.38	-
Weight			
Units: kilograms (kg)			
arithmetic mean	73.65	68.36	
standard deviation	± 15.986	± 14.661	-
Body Mass Index (BMI)			
Body Mass Index=weight/[height^2]			
Units: kg per square meter (kg/m^2)			
arithmetic mean	25.40	21.84	
standard deviation	± 5.080	± 3.580	-

End points

End points reporting groups

Reporting group title	Group 1: Vedolizumab IV 300 mg + Placebo
Reporting group description: Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 14, and 22, and vedolizumab placebo-matching, IV infusion once, at Week 10 to maintain the blind.	
Reporting group title	Group 2: Vedolizumab 300 mg
Reporting group description: Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 10, 14, and 22.	

Primary: Percentage of Participants with at Least 50% Reduction From Baseline in the Number of Draining Perianal Fistulae (of Those Draining at Baseline)

End point title	Percentage of Participants with at Least 50% Reduction From Baseline in the Number of Draining Perianal Fistulae (of Those Draining at Baseline) ^[1]
-----------------	---

End point description:

Closed fistulae are no longer draining despite gentle finger compression. Modified Full Analysis Set (mFAS) included all participants in FAS who had at least one draining fistula at baseline (Day 1). FAS included all randomized participants who received at least 1 dose of study medication and have a post baseline assessment of fistula healing. Data is reported for participants evaluable for this outcome measure.

End point type	Primary
----------------	---------

End point timeframe:

Day 1, Week 30

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 available for this endpoint.

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage of participants				
number (confidence interval 95%)	75.0 (50.5 to 99.5)	75.0 (45.0 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at Least 50% Reduction of from Baseline in the Number of Draining Perianal Fistulae (of Those Draining at Baseline) at Both Weeks 22 and 30

End point title	Percentage of Participants with at Least 50% Reduction of from Baseline in the Number of Draining Perianal Fistulae (of Those Draining at Baseline) at Both Weeks 22 and 30
-----------------	---

End point description:

Closed fistulae are no longer draining despite gentle finger compression. The mFAS includes all participants in the FAS who had at least one draining fistula at baseline (Day 1). The FAS includes all randomized participants who received at least 1 dose of study medication and have a post baseline assessment of fistula healing.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 22 and 30

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: percentage of participants				
number (confidence interval 95%)	72.7 (46.4 to 99.0)	62.5 (24.5 to 91.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with 100% Perianal Fistulae Closure (of the Fistulae Draining at Baseline)

End point title	Percentage of Participants with 100% Perianal Fistulae Closure (of the Fistulae Draining at Baseline)
-----------------	---

End point description:

Closed fistulae are no longer draining despite gentle finger compression. The mFAS included all participants in the FAS who had at least one draining fistula at baseline (Day 1). The FAS included all randomized participants who received at least 1 dose of study medication and have a post baseline assessment of fistula healing.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 30

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage of participants				
number (confidence interval 95%)	58.3 (30.4 to 86.2)	62.5 (24.5 to 91.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Perianal Fistulae Closure

End point title	Time to First Perianal Fistulae Closure
-----------------	---

End point description:

Closed fistulae are no longer draining despite gentle finger compression. The time to first fistula closure was analyzed descriptively using Kaplan-Meier product limit methods, with participants for which no fistula closure is reported being censored at the time of their last fistulae assessment or date of last record (Week 30 or early discontinuation). Estimated median time to fistula closure (and 95%CI) are reported. mFAS included participants in FAS with ≥ 1 draining fistula at baseline (Day 1). FAS included all randomized participants who received ≥ 1 dose of study drug, have a post-baseline assessment of fistula healing. 99999: Upper limit of 95% of confidence interval (CI) was not estimable due to low number of participant with events.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 30

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: days				
median (confidence interval 95%)	30.5 (15.0 to 71.0)	159.0 (16.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last (100%) Perianal Fistulae Closure

End point title	Time to Last (100%) Perianal Fistulae Closure
-----------------	---

End point description:

Closed fistulae are no longer draining despite gentle finger compression. The time to first fistula closure was analyzed descriptively using Kaplan-Meier product limit methods, with participants for which no fistula closure is reported being censored at the time of their last fistulae assessment or date of last record (Week 30 or early discontinuation). Estimated median time to fistula closure (and 95%CI) are reported. mFAS included participants in FAS with ≥ 1 draining fistula at baseline (Day 1). FAS included all randomized participants who received ≥ 1 dose of study drug, have a post-baseline assessment of fistula healing. 99999: Upper limit of 95% CI was not estimable due to low number of participant with events.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 30

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: days				
median (confidence interval 95%)	45.0 (15.0 to 155.0)	159.0 (16.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Perianal Fistulae Response

End point title	Duration of Perianal Fistulae Response
-----------------	--

End point description:

Duration of fistula response was measured by number of days with/without drainage. Duration of perianal fistula response (days) was derived as the sum of days with perianal fistula response between Day 1 and the end of the study (Week 30 or early discontinuation). Perianal fistula response is defined as reduction in the number of draining perianal fistulae (of those draining at Baseline) draining of at least 50%. The mFAS included all participants in the FAS who had at least one draining fistula at baseline (Day 1). The FAS included all randomized participants who received at least 1 dose of study medication and have a post-baseline assessment of fistula healing.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 30

End point values	Group 1: Vedolizumab IV 300 mg + Placebo	Group 2: Vedolizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: days				
median (full range (min-max))	158.5 (0 to 202)	33.5 (0 to 203)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 44 weeks

Adverse event reporting additional description:

At each visit investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by investigator was recorded, irrespective of relation to study treatment. Safety Analysis Set included all participants who received at least 1 dose of study medication.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	21.0
--------------------	------

Reporting groups

Reporting group title	Group 2: Vedolizumab 300 mg
-----------------------	-----------------------------

Reporting group description:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 10, 14, and 22.

Reporting group title	Group 1: Vedolizumab IV 300 mg + Placebo
-----------------------	--

Reporting group description:

Vedolizumab 300 mg, IV infusion, once, at Weeks 0, 2, 6, 14, and 22, and vedolizumab placebo-matching, IV infusion once, at Week 10 to maintain the blind.

Serious adverse events	Group 2: Vedolizumab 300 mg	Group 1: Vedolizumab IV 300 mg + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)	4 / 16 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 18 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group 2: Vedolizumab 300 mg	Group 1: Vedolizumab IV 300 mg + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	15 / 16 (93.75%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	4 / 18 (22.22%)	2 / 16 (12.50%)	
occurrences (all)	4	3	
Influenza like illness			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Catheter site bruise subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Granuloma subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Cough subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 16 (6.25%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Depression subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 16 (6.25%) 1	
Product issues Device expulsion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Device loosening subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Investigations			

C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Wound dehiscence subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 5	2 / 16 (12.50%) 2	
Migraine subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Lymphadenitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	

Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Gastrointestinal disorders Proctalgia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 16 (12.50%) 3	
Anorectal discomfort subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Rectal discharge subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Crohn's disease subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 5	1 / 16 (6.25%) 1	
Rectal stenosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 16 (6.25%) 1	
Abdominal distension subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Abdominal pain			

subjects affected / exposed	2 / 18 (11.11%)	4 / 16 (25.00%)	
occurrences (all)	2	4	
Abdominal tenderness			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dyschezia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Anal fistula			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	3	4	
Subileus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Oral pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			

Acne		
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)
occurrences (all)	1	1
Alopecia		
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Night sweats		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Dry skin		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Neutrophilic dermatosis		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Papule		
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Dermatitis		
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Eczema		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Neurodermatitis		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Erythema nodosum		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Dermatitis psoriasiform		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	0
Skin mass		
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1

Dermal cyst subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Skin striae subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Cutaneous vasculitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 3	
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 7	1 / 16 (6.25%) 1	
Myositis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 16 (12.50%) 2	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	
Back pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	

Tendon pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Spondylitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 18 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	4	
Anal fistula infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Campylobacter infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Fungal infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Perineal abscess			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2016	Amendment 1: •Requirements for perianal seton placement and seton removal were removed •Stratification factor was added for seton or no seton at randomization •Secondary endpoint to evaluate fistulas healed at both Week 22 and Week 30 was added •Modified inclusion criterion 6, 10, 11, exclusion criterion 6, 7, 17 and 19 per updated safety language and to remove the option of 5 half-lives as washout window, also some criteria were modified to allow additional types of antibiotics to reduce the incidence of abscess •Study sample size was reduced from 126 (63 per group) to 100 (50 per group) •Number of study sites were increased from 30 to 40 •Rationale for the proposed study was revised given that perianal seton replacement no longer required •Maximum dose of oral corticosteroids was changed from 30 to 20 mg/day.
20 April 2017	Amendment 5: •Requirement for perianal seton placement seton removal was removed, stratification factor was added for seton or no seton at randomization •Secondary endpoint to evaluate fistulas healed at both Week 22 and Week 30 was added •Modified inclusion criterion 6, 10, 11, exclusion criterion 6, 7, 17 and 19 per updated safety language and to remove the option of 5 half-lives as washout window, also some criteria were modified to allow additional types of antibiotic to reduce the incidence of abscess •Study sample size was reduced from 126 (63 per group) to 100 (50 per group) •Number of study sites were increased from 30 to 40. Rationale for the proposed study was revised given that perianal seton replacement no longer required •Schematic of Study Design was modified •Maximum dose of oral corticosteroids was changed from 30 to 20 mg/day.

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.

Takeda decided to close enrollment after randomizing 34 participants. Decision was taken due to challenges in recruitment and was not related to any safety concerns. Participants randomized before enrollment closure continued participation as planned.

Notes: