



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 | Investigator, Monitor, Subject, Carer, Data analyst |

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: