# Clinical trial results:
# An Open-Label, Multicenter, Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects with Moderate to Severe Crohn's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2010-020137-10 |
| Trial protocol | GB DE SE CZ AT ES FR BE IT NL HU LT |
| Global end of trial date | 05 January 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 December 2017 |
| First version publication date | 31 December 2017 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | M11-271 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01235689 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Abbvie Deutschland GmbH & Co.KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie Ltd., 011 800-633-9110, |
| Scientific contact | Anne Robinson, Pharm.D., AbbVie, anne.robinson@abbvie.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 | 03 January 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 05 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that tight control of disease activity, using stringent criteria based on Crohn's disease activity Index (CDAI), biomarkers (high sensitivity C-reactive protein [hs-CRP] and fecal calprotectin), and corticosteroid use, improves the rate of mucosal healing 48 weeks after randomization compared with management using less stringent criteria based only on CDAI and corticosteroid use.

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 November 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 31 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 38 |
| Country: Number of subjects enrolled | Czech Republic: 30 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Italy: 13 |
| Country: Number of subjects enrolled | Canada: 18 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | Romania: 12 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Switzerland: 8 |
| Country: Number of subjects enrolled | Turkey: 14 |

| | |
|---|---|
| Country: Number of subjects enrolled | Ukraine: 21 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Russian Federation: 3 |
| Worldwide total number of subjects | 252 |
| EEA total number of subjects | 178 |

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) | 248 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 59 sites in Canada, European Union, Israel, Japan, Russia, South Africa, Switzerland, Turkey, and the Ukraine.
The study included a screening period, up to 8 weeks of prednisone run-in treatment, a 48-week postrandomization treatment period, and a 70 day follow-up phone call or clinic visit.

### Pre-assignment

Screening details:

A total of 252 participants were enrolled and received study treatment, of whom
- 165 entered the prednisone run-in
  - 157 randomized (45 prior to Week 9, 112 at Week 9)
  - 8 discontinued prior to randomization.
- 87 randomized at Baseline.

Randomization was stratified by smoking status, weight, and disease duration.

### Pre-assignment period milestones[1]

| | |
|---|---|
| Number of subjects started | 252 |
| Intermediate milestone: Number of subjects | Entered prednisone run-in: 165 |
| Intermediate milestone: Number of subjects | Completed prednisone run-in: 157 |
| Number of subjects completed | 244 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | Lost to follow-up: 1 |
| Reason: Number of subjects | Use of prohibited drug: 1 |
| Reason: Number of subjects | Did not meet inclusion/exclusion criteria: 2 |
| Reason: Number of subjects | Pregnancy: 1 |
| Reason: Number of subjects | Adverse event, non-fatal: 2 |

Notes:

[1] - The number of subjects at the milestone is less than the number that completed the pre-assignment period. It is expected the number of subjects at the milestones will be greater than, or equal to the number that completed the pre-assignment period.
Justification: The Number Started indicates the total number of subjects enrolled in the study and the Number Completed indicates the number of subjects who were randomized. The intermediate milestones represent subjects who entered and completed the prednisone run-in phase prior to randomization.

### Period 1

| | |
|---|---|
| Period 1 title | Post-randomization Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |

| **Arm title** | Clinically Driven |
|---|---|

Arm description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI) and corticosteroid use.
Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified failure criteria using less stringent criteria:
At Key Visit 1 the criteria for management of disease activity were a CDAI decrease ≥ 70 (CR-70) compared to Baseline or CDAI < 200 at 1 week prior to the visit. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria for a change in treatment were a CDAI decrease of ≥ 100 (CR-100) compared to Baseline or CDAI < 200, and absence of prednisone during the preceding week.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Adalimumab |
| Investigational medicinal product code | ABT-D2E7 |
| Other name | Humira |
| Pharmaceutical forms | Suspension for injection in pre-filled injector |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

160 mg induction dose the first week, followed by 80 mg 2 weeks later, followed by 40 mg every other week as a maintenance dose. The dose of adalimumab was increased from 40 mg eow to 40 mg every week in participants with an inadequate response and de-escalated to 40 mg eow in participants who met success criteria.

| Investigational medicinal product name | Prednisone |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The suggested regimen for subjects initiating prednisone consists of a maximum dose of prednisone 40 mg/day for 2 weeks, followed by a fixed taper for 6 weeks.

| Investigational medicinal product name | Azathioprine |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with normal thiopurine methyltransferase (TPMT) enzyme activity could receive oral azathioprine 2.5 mg/kg/day. In participants with intermediate TPMT enzyme activity azathioprine was initiated at a dose of 1.25 mg/kg/day. The dose of azathioprine was adjusted according to abnormalities of white blood cell (WBC) count, platelet count, liver function tests (LFTs; i.e. alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase), lipase, blood urea nitrogen (BUN), and serum creatinine.

| **Arm title** | Tight Control |
|---|---|

Arm description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI), high sensitivity C-reactive protein (hs-CRP), fecal calprotectin, and corticosteroid use. Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified tight control criteria: At Key Visit 1 the success criteria were CDAI < 150, hs-CRP, < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone use. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria were CDAI < 150, hs-CRP < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone during the preceding week.

| Arm type | Experimental |
|---|---|

| | |
|---|---|
| Investigational medicinal product name | Adalimumab |
| Investigational medicinal product code | |
| Other name | Humira |
| Pharmaceutical forms | Suspension for injection in pre-filled injector |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

If adalimumab was initiated, it was administered subcutaneously as a 160 mg induction dose the first week, followed by 80 mg 2 weeks later, followed by 40 mg every other week as a maintenance dose. The dose of adalimumab was increased from 40 mg eow to 40 mg every week in participants with an inadequate response and de-escalated to 40 mg eow in participants who met success criteria.

| | |
|---|---|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The suggested regimen for participants initiating prednisone consisted of a maximum dose of prednisone 40 mg/day for 2 weeks, followed by a fixed taper for 6 weeks.

| | |
|---|---|
| Investigational medicinal product name | Azathioprine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with normal thiopurine methyltransferase (TPMT) enzyme activity could receive oral azathioprine 2.5 mg/kg/day. In participants with intermediate TPMT enzyme activity azathioprine was initiated at a dose of 1.25 mg/kg/day. The dose of azathioprine was adjusted according to abnormalities of white blood cell (WBC) count, platelet count, liver function tests (LFTs; i.e. alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase), lipase, blood urea nitrogen (BUN), and serum creatinine.

| **Number of subjects in period 1[2]** | Clinically Driven | Tight Control |
|---|---|---|
| Started | 122 | 122 |
| - Early Randomized (Baseline to Week 9) | 63 [3] | 69 [4] |
| - Randomized at Week 9 | 59 [5] | 53 [6] |
| Completed | 93 | 90 |
| Not completed | 29 | 32 |
| Consent withdrawn by subject | 3 | 4 |
| Adverse event, non-fatal | 12 | 16 |
| Miscellaneous | 1 | 5 |
| Lost to follow-up | 1 | 2 |
| Lack of efficacy | 12 | 5 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 252 participants were enrolled and received study treatment. Eighty-seven participants randomized prior to Week 9 and 165 participants entered the prednisone run-in, of whom

157 completed and randomized at Week 9 (total 244 randomized) and 8 discontinued.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subset of randomized subjects who were randomized from Baseline to Week 9.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subset of randomized subjects who were randomized from Baseline to Week 9.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subset of randomized subjects who randomized at Week 9.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subset of randomized subjects who randomized at Week 9.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Clinically Driven |

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI) and corticosteroid use.
Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified failure criteria using less stringent criteria:
At Key Visit 1 the criteria for management of disease activity were a CDAI decrease ≥ 70 (CR-70) compared to Baseline or CDAI < 200 at 1 week prior to the visit. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria for a change in treatment were a CDAI decrease of ≥ 100 (CR-100) compared to Baseline or CDAI < 200, and absence of prednisone during the preceding week.

| Reporting group title | Tight Control |
|---|---|

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI), high sensitivity C-reactive protein (hs-CRP), fecal calprotectin, and corticosteroid use. Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified tight control criteria: At Key Visit 1 the success criteria were CDAI < 150, hs-CRP, < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone use. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria were CDAI < 150, hs-CRP < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone during the preceding week.

| Reporting group values | Clinically Driven | Tight Control | Total |
|---|---|---|---|
| Number of subjects | 122 | 122 | 244 |
| Age categorical<br>Units: Subjects | | | |
| < 40 years | 97 | 96 | 193 |
| 40 to < 65 years | 23 | 24 | 47 |
| ≥ 65 years | 2 | 2 | 4 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 31.10 | 32.10 | |
| standard deviation | ± 11.40 | ± 11.97 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 69 | 72 | 141 |
| Male | 53 | 50 | 103 |
| Race<br>Units: Subjects | | | |
| White | 113 | 113 | 226 |
| Black | 2 | 3 | 5 |
| Asian | 3 | 2 | 5 |
| American Indian/Alaska Native | 0 | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| Multi-race | 1 | 1 | 2 |
| Other | 3 | 3 | 6 |

| | | | |
|---|---|---|---|
| Weight<br>Units: Subjects | | | |
| < 70 kg | 79 | 81 | 160 |
| ≥ 70 kg | 43 | 41 | 84 |
| Current Tobacco Use<br>Units: Subjects | | | |
| Yes | 33 | 31 | 64 |
| No | 89 | 91 | 180 |
| Disease Duration<br>Units: Subjects | | | |
| ≤ 2 years | 106 | 106 | 212 |
| > 2 years | 16 | 16 | 32 |
| Crohn's Disease Endoscopy Index of Severity (CDEIS) | | | |
| Measure Description: CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon (ileum, ascending colon, transverse colon, descending colon and sigmoid loop, and rectum). The score ranges from 0 to 44 where higher scores indicate more severe endoscopic activity. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 14.26 | 13.38 | |
| standard deviation | ± 6.925 | ± 6.049 | - |
| Crohn's Disease Activity Index (CDAI) | | | |
| CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. Participants were asked to record the frequency of stools, abdominal pain and general well-being on a daily basis. In addition to the diary data, the investigator assessed the following for the calculation of CDAI: presence of complications, the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is the sum of the products of each item multiplied by a weighting factor and generally ranges from 0 up to 600, where higher scores indicate more severe disease. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 267.7 | 273.3 | |
| standard deviation | ± 58.35 | ± 59.48 | - |

## End points

### End points reporting groups

| Reporting group title | Clinically Driven |
|---|---|

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI) and corticosteroid use.
Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified failure criteria using less stringent criteria:
At Key Visit 1 the criteria for management of disease activity were a CDAI decrease ≥ 70 (CR-70) compared to Baseline or CDAI < 200 at 1 week prior to the visit. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria for a change in treatment were a CDAI decrease of ≥ 100 (CR-100) compared to Baseline or CDAI < 200, and absence of prednisone during the preceding week.

| Reporting group title | Tight Control |
|---|---|

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI), high sensitivity C-reactive protein (hs-CRP), fecal calprotectin, and corticosteroid use. Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.
Participants who randomized at Week 9 meeting success criteria started with no therapy; participants who randomized prior to Week 9 or who randomized at Week 9 but did not meet the success criteria began treatment with adalimumab.
Therapy was escalated according to pre-specified tight control criteria: At Key Visit 1 the success criteria were CDAI < 150, hs-CRP, < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone use. At Key Visits 3, 4, and 5 (every 12 weeks after Key visit 1), the criteria were CDAI < 150, hs-CRP < 5 mg/L, fecal calprotectin < 250 µg/g, and absence of prednisone during the preceding week.

### Primary: Percentage of Participants With Mucosal Healing and No Deep Ulcerations

| End point title | Percentage of Participants With Mucosal Healing and No Deep Ulcerations |
|---|---|

End point description:

Percentage of participants with mucosal healing (defined as Crohn's disease endoscopy Index of severity [CDEIS] < 4) and no deep ulcerations on ileocolonoscopy (defined as the absence of all deep ulcerations in all segments explored in CDEIS) at 48 weeks after randomization (48 weeks after the 1st Key visit). The ileocolonoscopies were evaluated by the site.
CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon (ileum, ascending colon, transverse colon, descending colon and sigmoid loop, and rectum). The score ranges from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing data 48 weeks after Randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.3 | 45.9 | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Mucosal Healing and No Deep Ulceration |
|---|---|
| Comparison groups | Tight Control v Clinically Driven |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 [1] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[1] - Cochran-Mantel-Haenszel (CMH) test stratified by Screening smoking status (yes or no) and weight (< 70 kg or ≥ 70 kg).

## Secondary: Percentage of Participants in Deep Remission 48 Weeks After Randomization

| End point title | Percentage of Participants in Deep Remission 48 Weeks After Randomization |
|---|---|

End point description:

Deep remission was defined as CDAI < 150, discontinuation from steroids for at least 8 weeks, absence of draining fistula, CDEIS < 4 and no deep ulcerations.
CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. The score includes the frequency of stools, abdominal pain and general well-being as well as the presence of complications, use of antidiarrheals, presence of abdominal mass, hematocrit and weight. CDAI generally ranges from 0 to 600 where higher scores indicate more severe disease.
CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing data 48 weeks after randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 23.0 | 36.9 | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Deep Remission |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 [2] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[2] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Percentage of Participants in Biologic Remission 48 Weeks After Randomization

| End point title | Percentage of Participants in Biologic Remission 48 Weeks After Randomization |
|---|---|

End point description:

Biologic remission was defined as high sensitivity C-reactive protein (hs-CRP) < 5 mg/L, fecal Calprotectin < 250 µg/g, and CDEIS < 4 at 48 weeks after randomization.
CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing values 48 weeks after Randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 15.6 | 29.5 | | |

### Statistical analyses

| Statistical analysis title | Analysis of Biologic Remission |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 [3] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[3] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Percentage of Participants With Mucosal Healing 48 Weeks After Randomization

| End point title | Percentage of Participants With Mucosal Healing 48 Weeks |
|---|---|

| | |
|---|---|
| | After Randomization |

End point description:

Percentage of participants with mucosal healing (defined as a CDEIS < 4) at 48 weeks after randomization (48 weeks after the 1st Key visit). The ileocolonoscopies were evaluated by the site.
CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing values 48 weeks after Randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.3 | 45.9 | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of Mucosal Healing |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 [4] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[4] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Percentage of Participants With Mucosal Healing and CDEIS < 4 in Every Segment 48 Weeks After Randomization

| End point title | Percentage of Participants With Mucosal Healing and CDEIS < 4 in Every Segment 48 Weeks After Randomization |
|---|---|

End point description:

Percentage of participants with mucosal healing (defined as CDEIS < 4) and CDEIS < 4 in every segment on ileocolonoscopy at 48 weeks after randomization. The ileocolonoscopies were evaluated by the site.
CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing values 48 weeks after randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 23.8 | 29.5 | | |

### Statistical analyses

| Statistical analysis title | Analysis of Mucosal Healing and CDEIS < 4 |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.299 [5] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[5] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Percentage of Participants With Complete Mucosal Healing 48 Weeks After Randomization

| End point title | Percentage of Participants With Complete Mucosal Healing 48 Weeks After Randomization |
|---|---|

End point description:

Complete mucosal healing was defined as CDEIS = 0. CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing values 48 weeks after randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 16.4 | 18.0 | | |

### Statistical analyses

| Statistical analysis title | Analysis of Complete Mucosal Healing |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.728 [6] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[6] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Percentage of Participants With Endoscopic Response 48 Weeks After Randomization

| End point title | Percentage of Participants With Endoscopic Response 48 Weeks After Randomization |
|---|---|

End point description:

Endoscopic response was defined as a decrease CDEIS > 5 points. CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon. The range of the score is from 0 to 44 where higher scores indicate more severe endoscopic activity.
Participants with missing values 48 weeks after Randomization were counted as non-responders.

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

End point timeframe:

48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.2 | 50.8 | | |

### Statistical analyses

| Statistical analysis title | Analysis of Endoscopic Response |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.067 [7] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[7] - CMH test stratified by screening smoking status (yes or no) and weight (< 70 kg, ≥ 70 kg).

## Secondary: Change From Baseline in CDEIS at 48 Weeks After Randomization

| End point title | Change From Baseline in CDEIS at 48 Weeks After Randomization |
|---|---|

End point description:

CDEIS is an index for determining the severity of Crohn's disease. The CDEIS considers deep ulcerations, superficial ulcerations, ulcerated and non-ulcerated surface, and the presence of ulcerated/non-ulcerated stenosis evaluated in 5 pre-defined segments of the colon (ileum, ascending colon, transverse colon, descending colon and sigmoid loop, and rectum). The score ranges from 0 to 44 where higher scores indicate more severe endoscopic activity. A negative change from Baseline indicates improvement.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96[8] | 105[9] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -6.4 (± 7.69) | -7.7 (± 7.25) | | |

Notes:

[8] - Randomized participants with non-missing data at Baseline and 48 weeks after Randomization

[9] - Randomized participants with non-missing data at Baseline and 48 weeks after Randomization

### Statistical analyses

| **Statistical analysis title** | Analysis of Change From Baseline in CDEIS |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 201 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 [10] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 0.4 |

Notes:

[10] - Model included factors for treatment group, screening smoking status (yes or no), and weight (< 70 kg, ≥ 70 kg), and Baseline values as covariate.

## Secondary: Change From Baseline in CDAI Over Time

| End point title | Change From Baseline in CDAI Over Time |
|---|---|

End point description:

CDAI is used to quantify the symptoms of patients with Crohn's disease. Participants were asked to record the frequency of stools, abdominal pain and general well-being on a daily basis. In addition to the diary data, the investigator assessed the following for the calculation of CDAI: presence of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever), the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is the sum of the products of each item multiplied by a weighting factor and generally ranges from 0 up to 600, where remission of Crohn's disease is defined as CDAI < 150, and severe disease is defined as CDAI > 450. A negative change from Baseline indicates improvement.
CDAI was only measured at 14, 18, 26, 30, 38 and 42 weeks after randomization if a participant had

initiated a change in treatment.

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

End point timeframe:

Baseline and 4 and 8 weeks during the prednisone run-in, and 2, 6, 11, 14, 18, 23, 26, 30, 35, 38, 42, and 48 weeks after Randomization.

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122[11] | 122[12] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 of Prednisone Run-in (N = 79, 76) | -78.3 (± 80.02) | -90.9 (± 81.53) | | |
| Week 8 of Prednisone Run-in (N = 62, 54) | -64.2 (± 90.48) | -105.5 (± 88.40) | | |
| 2 Weeks After Randomization (N = 95, 110) | -80.2 (± 82.27) | -110.1 (± 85.06) | | |
| 6 Weeks After Randomization (N = 100, 110) | -93.1 (± 100.81) | -130.8 (± 89.40) | | |
| 11 Weeks After Randomization (N = 114, 115) | -103.5 (± 98.65) | -141.0 (± 97.82) | | |
| 14 Weeks After Randomization (N = 26, 16) | -71.1 (± 89.18) | -101.2 (± 115.90) | | |
| 18 Weeks After Randomization (N = 27, 16) | -69.9 (± 78.95) | -112.0 (± 115.01) | | |
| 23 Weeks After Randomization (N = 97, 107) | -143.3 (± 97.83) | -154.1 (± 101.63) | | |
| 26 Weeks After Randomization (N = 20, 42) | -71.8 (± 129.09) | -135.7 (± 112.43) | | |
| 30 Weeks After Randomization (N = 20, 42) | -47.9 (± 143.75) | -143.8 (± 103.54) | | |
| 35 Weeks After Randomization (N = 92, 95) | -140.4 (± 104.83) | -166.4 (± 93.12) | | |
| 38 Weeks After Randomization (N = 15, 19) | -60.8 (± 83.51) | -132.8 (± 103.15) | | |
| 42 Weeks After Randomization (N = 11, 16) | -76.8 (± 78.53) | -107.4 (± 99.19) | | |
| 48 Weeks After Randomization (N = 82, 90) | -146.2 (± 102.87) | -175.8 (± 97.69) | | |

Notes:

[11] - Randomized participants with non-missing data at each time point.

[12] - Randomized participants with non-missing data at each time point.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Crohn's Disease Flare

| End point title | Time to Crohn's Disease Flare |
|---|---|

End point description:

Time to Crohn's disease flare, where flare is defined as an increase in CDAI ≥ 70 points compared to Week 8 or Early Randomization CDAI, and a CDAI > 220.
"99999" indicates data that could not be estimated due to the low number of events.

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

End point timeframe:

From Randomization to 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Time to Crohn's Disease Flare |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.442 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.8 |

**Secondary: Time to Clinical Remission**

| End point title | Time to Clinical Remission |
|---|---|

End point description:

Clinical remission was defined as CDAI < 150. CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. The score includes the frequency of stools, abdominal pain and general well-being as well as the presence of complications, use of antidiarrheals, presence of abdominal mass, hematocrit and weight. CDAI scores generally range from 0 to 600 where higher scores indicate more severe disease.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 78 (28 to 163) | 43 (15 to 101) | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Time to Clinical Remission |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 1.9 |

**Secondary: Time to Steroid-free Remission**

| End point title | Time to Steroid-free Remission |
|---|---|

End point description:

Steroid-free remission was defined as CDAI < 150 and discontinuation from steroids for at least 8 weeks. CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. The score includes the frequency of stools, abdominal pain and general well-being as well as the presence of complications, use of antidiarrheals, presence of abdominal mass, hematocrit and weight. CDAI generally ranges from 0 to 600 where higher scores indicate more severe disease.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 162 (80 to 255) | 159 (78 to 168) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of Time to Steroid-free Remission |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.052 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.337 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.8 |

**Secondary: Percentage of Participants in Clinical Remission Over Time**

| End point title | Percentage of Participants in Clinical Remission Over Time |
|---|---|

End point description:

Clinical remission was defined as CDAI < 150. CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. The score includes the frequency of stools, abdominal pain and general well-being as well as the presence of complications, use of antidiarrheals, presence of abdominal mass, hematocrit and weight. CDAI generally ranges from 0 to 600 where higher scores indicate more severe disease. Participants with missing data at each time point were counted as non-responders. CDAI was only measured at 14, 18, 26, 30, 38 and 42 weeks after randomization if a participant had initiated a change in treatment.

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

End point timeframe:

Baseline and 4 and 8 weeks during the prednisone run-in, and 2, 6, 11, 14, 18, 23, 26, 30, 35, 38, 42, and 48 weeks after Randomization.

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of particiapnts | | | | |
| number (not applicable) | | | | |
| Week 4 of Prednisone Run-in | 24.6 | 30.3 | | |
| Week 8 of Prednisone Run-in | 14.8 | 22.1 | | |
| 2 Weeks After Randomization | 23.8 | 41.0 | | |
| 6 Weeks After Randomization | 32.8 | 47.5 | | |

| | | | | |
|---|---|---|---|---|
| 11 Weeks After Randomization | 41.8 | 62.3 | | |
| 14 Weeks After Randomization | 8.2 | 6.6 | | |
| 18 Weeks After Randomization | 9.0 | 8.2 | | |
| 23 Weeks After Randomization | 50.8 | 65.6 | | |
| 26 Weeks After Randomization | 4.1 | 20.5 | | |
| 30 Weeks After Randomization | 3.3 | 23.0 | | |
| 35 Weeks After Randomization | 45.1 | 59.8 | | |
| 38 Weeks After Randomization | 4.1 | 9.0 | | |
| 42 Weeks After Randomization | 4.1 | 7.4 | | |
| 48 Weeks After Randomization | 43.4 | 59.8 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants in Steroid-free Remission Over Time

| End point title | Percentage of Participants in Steroid-free Remission Over Time |
|---|---|

End point description:

Steroid-free remission was defined as CDAI < 150 and discontinuation from steroids for at least 8 weeks. CDAI is a tool used to quantify the symptoms of patients with Crohn's disease. The score includes the frequency of stools, abdominal pain and general well-being as well as the presence of complications, use of antidiarrheals, presence of abdominal mass, hematocrit and weight. CDAI generally ranges from 0 to 600 where higher scores indicate more severe disease.
Participants with missing data at each time point were counted as non-responders. CDAI was only measured at 14, 18, 26, 30, 38 and 42 weeks after randomization if a participant had initiated a change in treatment.

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

End point timeframe:

11, 14, 18, 23, 26, 30, 35, 38, 42, and 48 weeks after Randomization.

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| 11 Weeks After Randomization | 23.8 | 39.3 | | |
| 14 Weeks After Randomization | 4.1 | 4.9 | | |
| 18 Weeks After Randomization | 3.3 | 7.4 | | |
| 23 Weeks After Randomization | 45.1 | 63.1 | | |
| 26 Weeks After Randomization | 2.5 | 18.9 | | |
| 30 Weeks After Randomization | 0.8 | 21.3 | | |
| 35 Weeks After Randomization | 42.6 | 59.0 | | |
| 38 Weeks After Randomization | 4.1 | 9.0 | | |
| 42 Weeks After Randomization | 4.1 | 7.4 | | |
| 48 Weeks After Randomization | 39.3 | 59.8 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to All-cause Hospitalization

| | |
|---|---|
| End point title | Time to All-cause Hospitalization |

End point description:

Hospitalization was defined as a visit to hospital/clinic resulting in admission and overnight stay in hospital/clinic. "99999" indicates values that could not be estimated due to the low number of hospitalization events.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Analysis of Time to All-cause Hospitalization |
|---|---|
| Comparison groups | Tight Control v Clinically Driven |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.501 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.823 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.5 |

## Secondary: Time to Crohn's Disease-related Hospitalization or Hospitalization Due to Adverse Event Relating to Study Medication

| End point title | Time to Crohn's Disease-related Hospitalization or Hospitalization Due to Adverse Event Relating to Study Medication |
|---|---|

End point description:

Crohn's disease-related hospitalization was defined as a visit to hospital/clinic resulting in admission and overnight stay in hospital/clinic for reasons related to Crohn's disease (CD). Hospitalization for adverse events relating to study medication, i.e., prednisone, azathioprine or adalimumab, were according to Investigator's clinical judgment. "99999" indicates values that could not be estimated due to the low number of hospitalization events.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of Time to Hospitalization |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.459 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.785 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 1.5 |

## Secondary: Number of Major Crohn's Disease-related Surgeries After Randomization

| End point title | Number of Major Crohn's Disease-related Surgeries After Randomization |
|---|---|

End point description:

Major Crohn's disease-related intra-abdominal surgery included:
- bowel resection
- ostomy

• by-pass
• strictureplasty
• drainage of abdominal or pelvic abscess (surgical drainage or percutaneous drainage by interventional radiology).

The following were excluded:
• debridement
• exploration laparotomy
• abdominal surgery for other reason
• perineal related surgery
• abscess drainage
• placement of setons
• fistulotomy
• Total parental nutrition (TPN) use

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: surgeries | 3 | 6 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Crohn's Disease-related Hospitalizations After Randomization

| End point title | Number of Crohn's Disease-related Hospitalizations After Randomization |
|---|---|

End point description:

Any hospitalization with an overnight stay in hospital/clinic related to Crohn's disease.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: hospitalizations | 29 | 14 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of All-cause Hospitalizations After Randomization

| End point title | Number of All-cause Hospitalizations After Randomization |
|---|---|

End point description:

Hospitalization was defined as a visit to hospital/clinic resulting in admission and overnight stay in hospital/clinic.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: hospitalizations | 37 | 25 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Total Length of Stay in Hospital for All-cause Hospitalizations

| End point title | Total Length of Stay in Hospital for All-cause Hospitalizations |
|---|---|

End point description:

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26[13] | 22[14] | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 40.2 (± 45.72) | 50.1 (± 85.69) | | |

Notes:

[13] - Randomized participants with all-cause hospitalizations

[14] - Randomized participants with all-cause hospitalizations

### Statistical analyses

No statistical analyses for this end point

## Secondary: Total Length of Stay in Hospital for Crohn's Disease-related

## Hospitalizations

| End point title | Total Length of Stay in Hospital for Crohn's Disease-related Hospitalizations |
|---|---|

End point description:

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21[15] | 13[16] | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 9.8 (± 7.21) | 15.8 (± 20.39) | | |

Notes:

[15] - Randomized participants with Crohn's disease-related hospitalizations

[16] - Randomized participants with Crohn's disease-related hospitalizations

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Crohn's Disease-related Surgical Procedures After Randomization

| End point title | Number of Crohn's Disease-related Surgical Procedures After Randomization |
|---|---|

End point description:

The total number of CD-related surgical procedures included major CD-related surgery, debridement, perineal related surgery - abscess drainage, seton placement, fistulotomy, and TPN.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: surgical procedures | 9 | 7 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Crohn's Disease-related Hospitalization Due to Emergency

| End point title | Time to Crohn's Disease-related Hospitalization Due to Emergency |
|---|---|

End point description:

Hospitalization was defined as a visit to hospital/clinic resulting in admission and overnight stay in hospital/clinic. Hospitalization due to emergency was defined as a hospitalization admitted through the emergency department. "99999" indicates values that could not be estimated due to the low number of emergency hospitalizations.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

**Statistical analyses**

| **Statistical analysis title** | Time to Crohn's Emergency Hospitalization |
|---|---|
| Comparison groups | Clinically Driven v Tight Control |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.212 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.423 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 1.6 |

## Secondary: Number of Crohn's Disease-related Hospitalizations Due to Emergency

| End point title | Number of Crohn's Disease-related Hospitalizations Due to Emergency |
|---|---|

End point description:

Hospitalization was defined as a visit to hospital/clinic resulting in admission and overnight stay in hospital/clinic. Hospitalization due to emergency was defined as a hospitalization admitted through the emergency department.

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

End point timeframe:

From Randomization through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: emergency hospitalizations | 11 | 4 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Crohn's Disease Behavior According to Montreal Classification

| End point title | Change in Crohn's Disease Behavior According to Montreal Classification |
|---|---|

End point description:

Participants' Crohn's Disease was classified according to the Montreal Classification which classifies CD according to its predominant phenotypic elements (age at diagnosis, location, and disease behavior) based on the results of clinical examination and endoscopy.
Disease behavior was classified according to the following:
B1 = non-stricturing, non-penetrating; B2 = structuring; B3 = penetrating; P = perianal disease modifier.
The change in Montreal Classification is presented in three categories: no change, deterioration, and improvement. Deterioration was defined as an increase in behavior index between 1 and 3, or development of perianal disease. Participants with missing data at Week 48 were classified as deterioration.

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

End point timeframe:

From Baseline to 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: participants | | | | |
| Deterioration | 54 | 35 | | |
| No Change | 64 | 79 | | |
| Improvement | 4 | 8 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in High Sensitivity C-Reactive Protein (hs-CRP) Over Time

| End point title | Change From Baseline in High Sensitivity C-Reactive Protein |
|---|---|

| | |
|---|---|
| | (hs-CRP) Over Time |

End point description:

High sensitivity C-reactive protein was analyzed by a central laboratory. For participants with missing data after randomization last observation carried forward (LOCF) imputation was used.

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

End point timeframe:

Baseline and 8 weeks during the prednisone run-in, and 11, 23, 35, and 48 weeks after Randomization.

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 122 | | |
| Units: mg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 of Prednisone Run-in (N = 77, 73) | -10.3 (± 40.04) | -9.2 (± 33.67) | | |
| 11 Weeks After Randomization (N = 120, 121) | -14.6 (± 31.87) | -15.9 (± 26.38) | | |
| 23 Weeks After Randomization (N = 121, 122) | -15.1 (± 31.59) | -14.7 (± 28.94) | | |
| 35 Weeks After Randomization (N = 121, 122) | -11.0 (± 31.22) | -14.0 (± 28.85) | | |
| 48 Weeks After Randomization (N = 121, 122) | -12.3 (± 28.97) | -13.2 (± 28.93) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Fecal Calprotectin From Baseline to 48 Weeks After Randomization

| | |
|---|---|
| End point title | Change in Fecal Calprotectin From Baseline to 48 Weeks After Randomization |

End point description:

Stool samples were analyzed by a central laboratory for fecal calprotectin qualitative measurement (< 250 or ≥ 250 µg/g). Results are reported for participants in each category at Baseline and 48 weeks after Randomization.
Participants with missing data 48 weeks after Randomization were counted as having fecal calprotectin ≥ 250µg/g.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 120[17] | | |
| Units: participants | | | | |
| Baseline < 250µg/g and Week 48 < 250µg/g | 8 | 14 | | |
| Baseline < 250µg/g and Week 48 ≥ 250µg/g | 9 | 10 | | |
| Baseline ≥ 250µg/g and Week 48 < 250µg/g | 37 | 44 | | |
| Baseline ≥ 250µg/g and Week 48 ≥ 250µg/g | 68 | 52 | | |

Notes:

[17] - Randomized participants with Baseline data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Total Dose of Prednisone

| End point title | Total Dose of Prednisone |
|---|---|

End point description:

The total dose of prednisone each participant received during both the run-in phase and post-randomization treatment phase.

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

End point timeframe:

From Baseline through 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102[18] | 104[19] | | |
| Units: mg | | | | |
| arithmetic mean (standard deviation) | 1505.7 (± 1029.83) | 1369.8 (± 1137.65) | | |

Notes:

[18] - Participants who received prednisone

[19] - Participants who received prednisone

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score

| End point title | Change From Baseline in Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score |
|---|---|

End point description:

The IBDQ measures the effects of inflammatory bowel disease on daily function and quality of life. The IBDQ consists of 32 questions which address symptoms as a result of Crohn's disease, feeling in general, and mood. Each question is answered on a scale from 1 (all of the time) to 7 ( none of the

time); the total score ranges from 7 (worst) to 224 (best). A positive change from baseline indicates improvement.
Last observation carried forward imputation was used.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 111[20] | 111[21] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 31.2 (± 39.33) | 41.9 (± 36.90) | | |

Notes:

[20] - Randomized participants with baseline and at least one post-baseline value

[21] - Randomized participants with baseline and at least one post-baseline value

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Work Productivity Activity Index - Crohn's Disease (WPAI:CD)

| End point title | Change From Baseline in Work Productivity Activity Index - Crohn's Disease (WPAI:CD) |
|---|---|

End point description:

The WPAI:CD questionnaire was used to assess impairments in paid work and unpaid work due to symptoms of Crohn's Disease. The self-administered questionnaire consisted of 6 questions.
Work time missed is defined as the percentage of time absent from work due to Crohn's disease in the past week.
Impairment while working is the degree to which Crohn's disease affected productivity while working in the past 7 days.
Total work productivity impairment takes into account both hours missed due to Crohn's disease symptoms and the degree to which Crohn's disease affected productivity while working.
Total activity impairment is the percent impairment of non-work related activities due to Crohn's disease.
WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. A negative change from Baseline indicates improvement.
LOCF imputation was used. The first 3 scores were only calculated for participants who were employed.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| **End point values** | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 119[22] | 118[23] | | |
| Units: percent impairment | | | | |
| arithmetic mean (standard deviation) | | | | |
| Work time missed (N = 67, 62) | -12.8 (± 30.17) | -17.6 (± 41.33) | | |

| | | | | |
|---|---|---|---|---|
| Impairment while working (N = 64, 52) | -17.5 (± 23.37) | -25.8 (± 34.32) | | |
| Overall work impairment (n = 67, 62) | -21.7 (± 29.68) | -29.2 (± 39.53) | | |
| Activity impairment (N = 118, 118) | -19.2 (± 27.16) | -27.7 (± 33.22) | | |

Notes:

[22] - Randomized participants with baseline and at least one post-baseline value

[23] - Randomized participants with baseline and at least one post-baseline value

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Patient Health Questionnaire - 9 (PHQ9)

| End point title | Change From Baseline in Patient Health Questionnaire - 9 (PHQ9) |
|---|---|

End point description:

The PHQ-9 is a 9-item questionnaire for assessing the severity of depression. Each question is answered on a scale from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27, where higher scores indicate more severe depression. A negative change from Baseline score indicates improvement. LOCF imputation was used.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120[24] | 120[25] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -3.6 (± 5.65) | -5.6 (± 5.95) | | |

Notes:

[24] - Randomized participants with Baseline and at least one post-baseline value

[25] - Randomized participants with Baseline and at least one post-baseline value

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score

| End point title | Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score |
|---|---|

End point description:

The FACIT-Fatigue scale is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, from 0 (not at all) to 4 (very much). The FACIT-Fatigue score ranges from 0 to 52, with higher scores denoting lower levels of fatigue.
A positive change from Baseline score indicates an improvement. LOCF imputation was used.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120[26] | 119[27] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 7.6 (± 10.85) | 13.0 (± 13.19) | | |

Notes:

[26] - Randomized participants with Baseline and at least 1 post-baseline value

[27] - Randomized participants with Baseline and at least 1 post-baseline value

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Short-Form 36 (SF-36) Physical Component Summary and Mental Component Summary Scores

| End point title | Change From Baseline in Short-Form 36 (SF-36) Physical Component Summary and Mental Component Summary Scores |
|---|---|

End point description:

The Medical Outcome Study Short Form 36-Item Health Survey (SF-36), Version 2 is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health).
The physical component summary (PCS) score summarizes the subscales physical functioning, role-physical, bodily pain, and general health. The mental component summary (MCS) score summarizes the subscales vitality, social functioning, role-emotional, and mental health. Each score ranges from 0 to 100 where higher scores indicate a better quality of life. A positive change from Baseline score indicates an improvement.
LOCF imputation was used.

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

End point timeframe:

Baseline and 48 weeks after Randomization

| End point values | Clinically Driven | Tight Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 119[28] | 118[29] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Component Summary Score | 6.3 (± 8.34) | 9.2 (± 10.22) | | |
| Mental Component Summary Score | 5.8 (± 12.24) | 9.3 (± 12.40) | | |

Notes:

[28] - Randomized participants with Baseline and at least one post-baseline value

[29] - Randomized participants with Baseline and at least one post-baseline value

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from randomization until 70 days after the last dose of study drug (up to 58 weeks).

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any adverse event or serious adverse event that begins or worsens in severity on or after randomization until 70 days after the last dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Clinically Driven |

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI) and corticosteroid use.
Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.

| | |
|---|---|
| Reporting group title | Tight Control |

Reporting group description:

Participants randomized to receive management of disease activity using criteria based on Crohn's Disease Activity Index (CDAI), high sensitivity C-reactive protein (hs-CRP), fecal calprotectin, and corticosteroid use. Participants received customized therapy that could include prednisone, adalimumab, and azathioprine.

| Serious adverse events | Clinically Driven | Tight Control | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 122 (20.49%) | 22 / 122 (18.03%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| C-Reactive Protein Increased | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholesteatoma | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Cartilage Injury | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus Fracture | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus Injury | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Guillain-Barre Syndrome | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial Venous Sinus Thrombosis | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Drug Intolerance | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Distension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | 2 / 122 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal Fistula | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's Disease | | | |
| subjects affected / exposed | 12 / 122 (9.84%) | 6 / 122 (4.92%) | |
| occurrences causally related to treatment / all | 1 / 13 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula of Small Intestine | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileal Stenosis | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 2 / 122 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malocclusion | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal Perforation | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small Intestinal Obstruction | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal Septum Disorder | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| 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 | | | |
| Erythema Nodosum | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Retrognathia | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator Cuff Syndrome | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (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 | | | |
| Abdominal Abscess | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 2 / 122 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 122 (0.82%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal Abscess | | | |
| subjects affected / exposed | 4 / 122 (3.28%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium Difficile Infection | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 2 / 122 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis Salmonella | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis Viral | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal Vestibulitis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Tuberculosis | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 1 / 122 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotavirus Infection | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (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 | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viraemia | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 0 / 122 (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: 5 %

| **Non-serious adverse events** | Clinically Driven | Tight Control | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 78 / 122 (63.93%) | 76 / 122 (62.30%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 122 (5.74%) | 7 / 122 (5.74%) | |
| occurrences (all) | 7 | 9 | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 122 (12.30%) | 18 / 122 (14.75%) | |
| occurrences (all) | 24 | 23 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 122 (5.74%) | 8 / 122 (6.56%) | |
| occurrences (all) | 8 | 8 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 11 / 122 (9.02%) | 11 / 122 (9.02%) | |
| occurrences (all) | 13 | 14 | |
| Injection Site Erythema | | | |
| subjects affected / exposed | 0 / 122 (0.00%) | 8 / 122 (6.56%) | |
| occurrences (all) | 0 | 10 | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 122 (9.84%) | 9 / 122 (7.38%) | |
| occurrences (all) | 16 | 12 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 15 / 122 (12.30%) | 13 / 122 (10.66%) | |
| occurrences (all) | 18 | 20 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 4 / 122 (3.28%) | 8 / 122 (6.56%) | |
| occurrences (all) | 4 | 9 | |
| Crohn'S Disease | | | |
| subjects affected / exposed | 23 / 122 (18.85%) | 11 / 122 (9.02%) | |
| occurrences (all) | 26 | 15 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | 10 / 122 (8.20%) | |
| occurrences (all) | 2 | 12 | |
| Nausea | | | |
| subjects affected / exposed | 7 / 122 (5.74%) | 21 / 122 (17.21%) | |
| occurrences (all) | 10 | 23 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 122 (3.28%) | 13 / 122 (10.66%) | |
| occurrences (all) | 6 | 14 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 7 / 122 (5.74%) | 7 / 122 (5.74%) | |
| occurrences (all) | 7 | 9 | |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 10 / 122 (8.20%) | 4 / 122 (3.28%) | |
| occurrences (all) | 11 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 8 / 122 (6.56%) | 5 / 122 (4.10%) | |
| occurrences (all) | 8 | 6 | |
| Rash | | | |
| subjects affected / exposed | 9 / 122 (7.38%) | 4 / 122 (3.28%) | |
| occurrences (all) | 12 | 4 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 19 / 122 (15.57%) | 17 / 122 (13.93%) | |
| occurrences (all) | 20 | 20 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 8 / 122 (6.56%) | 7 / 122 (5.74%) | |
| occurrences (all) | 10 | 8 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 122 (14.75%) | 18 / 122 (14.75%) | |
| occurrences (all) | 24 | 22 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | 7 / 122 (5.74%) | |
| occurrences (all) | 1 | 7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 August 2010 | • Removed SES CD and reference to the publication.<br>• Added subjects who met success criteria at Week 9 Key visit to the list of subjects who went directly to TO2.<br>• Specified that subjects within the rescue Therapeutic Option 4 could restart prednisone under certain conditions.<br>• Specified that subjects who re-escalated in TO3 success or Therapeutic Option 4 success were to remain in either TO3 or TO4 of their allocated arm.<br>• Clarified that the prednisone re initiation based on CDAI > 300 in Therapeutic Option 4 only occurred upon the first entry into TO4.<br>• Included that budesonide and systemic corticosteroid with CD related corticosteroids that were to be recorded regardless of when they were taken.<br>• Updated study activities table to clarify situations that required an unscheduled visit; remove retesting fecal calprotectin if elevated for reasons other than CD; clarify that a stool sample was to be obtained at an unscheduled visit for a flare to determine fecal calprotectin levels; clarify that the 70 day follow-up was not required for subjects who continued on adalimumab therapy after the end of study participation.<br>• Added pleural thickening and signs of active TB for standard evaluations.<br>• Added that retesting of elevated fecal calprotectin levels was not required and that the investigator may delay success criteria visit for suspected infection. |
| 16 March 2011 | • Clarified and modified required (onsite and telephone follow-up) versus optional visits.<br>• Stated that an ET endoscopy was not to be performed if the subject discontinued early prior to randomization.<br>• Added that QuantiFERON TB Gold test or equivalent was an acceptable alternative to the PPD test for TB screening at the screening visit and at subsequent visits if required by local guidelines, including visits for flare and unsatisfactory response to therapy.<br>• Modified rules for a subject to move to the Rescue Group after randomization.<br>• Stated that calculation of CD3S was to be a substudy. Added that ET MRIs were not to be performed if a subject discontinued early prior to randomization.<br>• Allowed a subject to have either elevated hs CRP or fecal calprotectin to be eligible for the study<br>• Clarified that subjects must have not been taking immunomodulator(s) for non CD use at Baseline.<br>• Modified current and previous corticosteroid/budesonide use criteria.<br>• Removed the exclusion criterion for subjects not on stable doses of aminosalicylates, CD related antibiotics, and topical therapy for CD prior to Baseline.<br>• Updated dysplasia exclusion criterion to include information for endoscopy performed independent of the study.<br>• Modified MRI contraindications and impaired renal function to apply only to subjects who consented to participate in the CD3S (MRI) substudy.<br>• Updated rationale and include prohibition of allopurinol due to interference with AZA.<br>• Removed active and chronic hepatitis B and added exclusions of viral infections and positive hepatitis B tests.<br>• Added that subjects were to have an additional visit occurring 4 weeks after initiating AZA as required per local requirements. |

| | |
|---|---|
| 29 September 2011 | • Change references to end of study visit, if not an ET visit, from Week 56 to 48 weeks after randomization.<br>• Update primary objective timeline to approximately 1 year (56 weeks).<br>• Modify entry CDAI score based on whether subject was receiving prednisone or equivalent and dose of prednisone received ≥ 7 days prior to Baseline.<br>• Allow randomization at Baseline in subjects with active disease or for whom prednisone or equivalent had to be tapered according to investigator's opinion AND who had received corticosteroids for ≥ 4 weeks, including 2 weeks of prednisone or equivalent.<br>• Modify success criteria in the Clinically Driven group.<br>• Modify Rescue Group entry from flare or unsatisfactory response.<br>• Modify CD intestinal locations to include isolated ileal disease, clarify that colonic includes the rectum, and increase disease duration to ≤ 6 years.<br>• Change total CDEIS score from > 8 to > 6 and timing of entry criteria endoscopy from within 3 weeks prior to Baseline to Screening.<br>• Modify TPMT enzyme activity cutoff from ≤ 67 mU/L to ≤ 20 mU/L and specify that subjects with intermediate enzyme activity were to undergo weekly laboratory surveillance for ≥ 4 weeks per local guidelines, if initiating TO 4.<br>• Add stricture exclusion for subjects were with a passable stricture, even if it could be dilated during the screening endoscopy.<br>• Add exclusion for subjects with recent surgery (< 6 months of screening).<br>• Delete exclusion for subjects who underwent therapeutic enemas within 2 months of Baseline.<br>• Allow prescreening endoscopies within 4 weeks of Baseline instead of 3 weeks, also allow documentation with photographs instead of recordings if CDEIS was evaluated during the endoscopy. Allow rescreening subjects to avoid a second endoscopy for an initial screen failure not due to an ineligible CDEIS, if the time period between rescreen and randomization was ≤ 12 weeks.<br>• Allow subjects with intermediate TPMT to initiate AZA at a lower dose |
| 21 March 2013 | • Updated requirements and study schedule for Rescue Group entry and for subjects who needed to escalate therapy within the Rescue Group between scheduled visits.<br>• Included Janus kinase (JAK) and alpha-integrin inhibitors to exclusion criteria. |
| 28 January 2015 | • Modified TB language to add the possibility of including subjects who had evidence of a latent TB infection under certain circumstances. An annual TB test was to be performed for all subjects who completed the study.<br>• Clarified for Montreal Classification that imaging needed to be available to consider a stricture as inflammatory.<br>• Included prohibited new treatments available for CD and cytopheresis therapy (sometimes used in Japan for treatment of CD). |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported