# Clinical trial results:
# A Phase 2, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of apremilast (CC-10004) for treatment of subjects with active ulcerative colitis.

## Summary

| | |
|---|---|
| EudraCT number | 2014-002981-64 |
| Trial protocol | CZ BG IT |
| Global end of trial date | 03 June 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 March 2020 |
| First version publication date | 13 March 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CC-10004-UC-001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02289417 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 86 Morris Avenue, Summit, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com |
| Scientific contact | Denesh Chitkara, Celgene Corporation, 01 908-897-5751, dchitkara@celgene.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 June 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of apremilast (30 mg twice daily [BID] and 40 mg BID), compared with placebo, in subjects with active ulcerative colitis (UC).

Protection of trial subjects:

Patient Confidentiality, Informed Consent, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 08 January 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 1 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 9 |
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | Czech Republic: 6 |
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Poland: 36 |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | Ukraine: 13 |
| Country: Number of subjects enrolled | United States: 41 |
| Country: Number of subjects enrolled | New Zealand: 3 |
| Worldwide total number of subjects | 170 |
| EEA total number of subjects | 99 |

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) | 158 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 61 sites in Australia (3 sites) and New Zealand (1 site); Bulgaria (6 sites), Czech Republic (2 sites), Hungary (3 sites), Poland (9 sites), Russia (1 site), and Ukraine (10 sites); Canada (2 sites) and United States (13 sites); and France (4 sites), Germany (1 site), Italy (4 sites), and the Netherlands (2 sites).

### Pre-assignment

Screening details:

A total of 170 participants were randomized in a 1:1:1 ratio and received apremilast (30 mg BID or 40 mg BID), or identically appearing placebo and stratified based on concomitant use of oral corticosteroids and previous exposure to immunosuppressants.

### Period 1

| | |
|---|---|
| Period 1 title | Placebo-Controlled Phase Weeks 0-12 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer |

Blinding implementation details:

The blind was not to be broken during the study unless, in the opinion of the investigator, it was necessary to safely treat the subject. The decision to break the blind in emergency situations was the responsibility of the treating physician, which was not be delayed or refused by the sponsor. However, the investigator could contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsules (identical in appearance to apremilast) BID.

| | |
|---|---|
| **Arm title** | Apremilast 30 mg |

Arm description:

Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg capsules BID

| **Arm title** | Apremilast 40 mg |
|---|---|

Arm description:

Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 40 mg capsules BID

| **Number of subjects in period 1** | Placebo | Apremilast 30 mg | Apremilast 40 mg |
|---|---|---|---|
| Started | 58 | 57 | 55 |
| Completed | 51 | 53 | 52 |
| Not completed | 7 | 4 | 3 |
| Consent withdrawn by subject | 1 | 3 | 2 |
| Adverse event, non-fatal | 3 | - | 1 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | 3 | - | - |

## Period 2

| Period 2 title | Active Treatment Phase Weeks 12-52 |
|---|---|
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

The blind was not to be broken during the study unless, in the opinion of the investigator, it was necessary to safely treat the subject. The decision to break the blind in emergency situations was the responsibility of the treating physician, which was not be delayed or refused by the sponsor. However, the investigator could contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Placebo/Apremilast 30 mg |

Arm description:

Participants initially randomized to placebo capsules in the placebo-controlled period were re-randomized at week 12 to receive 30 mg apremilast capsules BID for 40 weeks during the active treatment phase.

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

| | |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg capsules BID.

| | |
|---|---|
| **Arm title** | Placebo/Apremilast 40 mg |

Arm description:

Participants initially randomized to placebo in the placebo-controlled period were re-randomized at week 12 to receive 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 40 mg capsules BID.

| | |
|---|---|
| **Arm title** | Apremilast 30 mg/Apremilast 30 mg |

Arm description:

Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. At week 12, participants who achieved at least a 20% decrease from baseline in the total Mayo score (TMS) continued to receive 30 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg capsules BID.

| | |
|---|---|
| **Arm title** | Apremilast 30 mg/ Apremilast 40 mg |

Arm description:

Participants initially randomized to 30 mg apremilast capsules BID in the placebo-controlled phase who did not achieve at least 20% decrease in the TMS were re-assigned to 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 40 mg capsules BID.

| | |
|---|---|
| **Arm title** | Apremilast 40 mg/Apremilast 40 mg |

Arm description:

Participants initially randomized to 40 mg apremilast capsules BID in the placebo-controlled phase continued to receive 40 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase, regardless of achieving a 20% decrease in TMS or not.

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

| | |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:
Apremilast 40 mg capsules BID.

| | |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:
Apremilast 40 mg capsules BID.

| **Number of subjects in period 2** | Placebo/Apremilast 30 mg | Placebo/Apremilast 40 mg | Apremilast 30 mg/Apremilast 30 mg |
|---|---|---|---|
| Started | 26 | 25 | 41 |
| Completed | 17 | 20 | 39 |
| Not completed | 9 | 5 | 2 |
| Consent withdrawn by subject | - | 1 | - |
| Adverse event, non-fatal | 2 | 2 | 1 |
| Miscellaneous | 1 | - | - |
| Pregnancy | - | - | - |
| Lost to follow-up | - | - | - |
| Lack of efficacy | 6 | 2 | 1 |

| **Number of subjects in period 2** | Apremilast 30 mg/ Apremilast 40 mg | Apremilast 40 mg/Apremilast 40 mg |
|---|---|---|
| Started | 12 | 52 |
| Completed | 7 | 39 |
| Not completed | 5 | 13 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 1 | 4 |
| Miscellaneous | - | 1 |
| Pregnancy | - | 1 |
| Lost to follow-up | - | 1 |
| Lack of efficacy | 3 | 5 |

## Period 3

| | |
|---|---|
| Period 3 title | Extension Phase Weeks 52-104 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Extension Phase: Apremilast 30 mg |

Arm description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 30 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg capsules BID

| | |
|---|---|
| **Arm title** | Extension Phase Apremilast 40 mg |

Arm description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 40 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla; CC-10004 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 40 mg capsules BID

| **Number of subjects in period 3[1]** | Extension Phase: Apremilast 30 mg | Extension Phase Apremilast 40 mg |
|---|---|---|
| Started | 45 | 54 |
| Completed | 38 | 48 |
| Not completed | 7 | 6 |
| Consent withdrawn by subject | 2 | 1 |
| Adverse event, non-fatal | 2 | 3 |
| Miscellaneous | 1 | - |
| Lack of efficacy | 2 | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects advanced to the next phase either by choice or due to disease.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase. | |
| Reporting group title | Apremilast 30 mg |
| Reporting group description: | |
| Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. | |
| Reporting group title | Apremilast 40 mg |
| Reporting group description: | |
| Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. | |

| Reporting group values | Placebo | Apremilast 30 mg | Apremilast 40 mg |
|---|---|---|---|
| Number of subjects | 58 | 57 | 55 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 54 | 54 | 50 |
| From 65-84 years | 4 | 3 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 42.9 | 40.1 | 43.4 |
| standard deviation | ± 14.04 | ± 13.50 | ± 14.92 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 25 | 18 | 21 |
| Male | 33 | 39 | 34 |
| Race<br>Units: Subjects | | | |
| Asian | 0 | 0 | 1 |
| White | 54 | 52 | 45 |
| Other | 1 | 1 | 1 |
| Not Reported or Collected | 3 | 4 | 8 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 1 | 5 |
| Not Hispanic or Latino | 55 | 54 | 46 |
| Unknown or Not Reported | 1 | 2 | 4 |
| Baseline Use of Oral Corticosteroids<br>Units: Subjects | | | |
| Use of Baseline Corticosteroids | 17 | 14 | 12 |
| Non-Use of Corticosteroids | 41 | 43 | 43 |
| Previous Exposure to Immunosuppressants<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Previous Exposure to Immunosuppressants | 17 | 18 | 16 |
| No Previous Exposure to Immunosuppressants | 41 | 39 | 39 |
| Duration of Ulcerative Colitis | | | |
| Units: Years | | | |
| arithmetic mean | 6.85 | 6.15 | 8.63 |
| standard deviation | ± 7.043 | ± 5.432 | ± 10.278 |
| Baseline Total Mayo Score (TMS) | | | |
| The TMS is an instrument designed to measure disease activity of Ulcerative Colitis (UC). The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease: • Stool Frequency Subscore (SFS) • Rectal Bleeding Subscore (RBS) • Endoscopy Subscore • Physician's Global Assessment (PGA) | | | |
| Units: units on a scale | | | |
| arithmetic mean | 8.2 | 8.5 | 8.1 |
| standard deviation | ± 1.68 | ± 1.62 | ± 1.67 |
| Modified Mayo Score (MMS) | | | |
| The MMS was based on the stool frequency, rectal bleeding and endoscopy subscores of the total Mayo score, and excluded the Physician's Global subscore, since this was a global measure that is subjective in nature. The MMS range from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 6.1 | 6.4 | 6.0 |
| standard deviation | ± 1.51 | ± 1.48 | ± 1.47 |
| Partial Mayo Score (PMS) | | | |
| The partial Mayo score is the sum of the rectal bleeding score, the stool frequency score and the physician's global assessment. The partial Mayo score range is from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms and assessment. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 5.6 | 5.8 | 5.5 |
| standard deviation | ± 1.46 | ± 1.44 | ± 1.57 |
| Mayo Endoscopic Subscore (MES) | | | |
| The Mayo endoscopy subscore findings are defined as: 0 = Normal or inactive disease 1 = Mild Disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 2.6 | 2.7 | 2.6 |
| standard deviation | ± 0.49 | ± 0.45 | ± 0.49 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 170 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 158 | | |
| From 65-84 years | 12 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 64 | | |
| Male | 106 | | |

| | | | |
|---|---|---|---|
| Race<br>Units: Subjects | | | |
| Asian | 1 | | |
| White | 151 | | |
| Other | 3 | | |
| Not Reported or Collected | 15 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 8 | | |
| Not Hispanic or Latino | 155 | | |
| Unknown or Not Reported | 7 | | |
| Baseline Use of Oral Corticosteroids<br>Units: Subjects | | | |
| Use of Baseline Corticosteroids | 43 | | |
| Non-Use of Corticosteroids | 127 | | |
| Previous Exposure to Immunosuppressants<br>Units: Subjects | | | |
| Previous Exposure to Immunosuppressants | 51 | | |
| No Previous Exposure to Immunosuppressants | 119 | | |
| Duration of Ulcerative Colitis<br>Units: Years<br>arithmetic mean<br>standard deviation | -- | | |
| Baseline Total Mayo Score (TMS) | | | |
| The TMS is an instrument designed to measure disease activity of Ulcerative Colitis (UC). The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease: • Stool Frequency Subscore (SFS) • Rectal Bleeding Subscore (RBS) • Endoscopy Subscore • Physician's Global Assessment (PGA) | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -- | | |
| Modified Mayo Score (MMS) | | | |
| The MMS was based on the stool frequency, rectal bleeding and endoscopy subscores of the total Mayo score, and excluded the Physician's Global subscore, since this was a global measure that is subjective in nature. The MMS range from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms. | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -- | | |
| Partial Mayo Score (PMS) | | | |
| The partial Mayo score is the sum of the rectal bleeding score, the stool frequency score and the physician's global assessment. The partial Mayo score range is from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms and assessment. | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -- | | |
| Mayo Endoscopic Subscore (MES) | | | |
| The Mayo endoscopy subscore findings are defined as: 0 = Normal or inactive disease 1 = Mild Disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration). | | | |
| Units: units on a scale<br>arithmetic mean | | | |

| | | | |
|---|---|---|---|
| standard deviation | - | | |

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase. | |
| Reporting group title | Apremilast 30 mg |
| Reporting group description: | |
| Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. | |
| Reporting group title | Apremilast 40 mg |
| Reporting group description: | |
| Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. | |
| Reporting group title | Placebo/Apremilast 30 mg |
| Reporting group description: | |
| Participants initially randomized to placebo capsules in the placebo-controlled period were re-randomized at week 12 to receive 30 mg apremilast capsules BID for 40 weeks during the active treatment phase. | |
| Reporting group title | Placebo/Apremilast 40 mg |
| Reporting group description: | |
| Participants initially randomized to placebo in the placebo-controlled period were re-randomized at week 12 to receive 40 mg apremilast capsules BID for 40 weeks during the active treatment phase. | |
| Reporting group title | Apremilast 30 mg/Apremilast 30 mg |
| Reporting group description: | |
| Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. At week 12, participants who achieved at least a 20% decrease from baseline in the total Mayo score (TMS) continued to receive 30 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase. | |
| Reporting group title | Apremilast 30 mg/ Apremilast 40 mg |
| Reporting group description: | |
| Participants initially randomized to 30 mg apremilast capsules BID in the placebo-controlled phase who did not achieve at least 20% decrease in the TMS were re-assigned to 40 mg apremilast capsules BID for 40 weeks during the active treatment phase. | |
| Reporting group title | Apremilast 40 mg/Apremilast 40 mg |
| Reporting group description: | |
| Participants initially randomized to 40 mg apremilast capsules BID in the placebo-controlled phase continued to receive 40 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase, regardless of achieving a 20% decrease in TMS or not. | |
| Reporting group title | Extension Phase: Apremilast 30 mg |
| Reporting group description: | |
| Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 30 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4. | |
| Reporting group title | Extension Phase Apremilast 40 mg |
| Reporting group description: | |
| Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 40 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase. | |
| Subject analysis set title | Apremilast 30 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

TEAEs during the apremilast 30 mg BID treatment for participants who received 30 mg apremilast capsules BID only and participants who initially received 30 mg apremilast capsules BID and switched to 40 mg apremilast capsules BID at Week 12, and participants who initially received placebo capsules BID and switched to 30 mg apremilast capsules BID at Week 12.

| | |
|---|---|
| Subject analysis set title | Apremilast 40 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

TEAEs during the apremilast 40 mg BID treatment for participants who received 40 mg apremilast capsules BID only, and participants who initially received placebo BID and switched to 40 mg apremilast capsules BID at Week 12.

| | |
|---|---|
| Subject analysis set title | Apremilast 30 mg/Apremilast 40 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

TEAEs during the apremilast 40 mg BID treatment for participants who initially received 30 mg apremilast BID and switched to 40 mg apremilast BID at Week 12.

| | |
|---|---|
| Subject analysis set title | Extension Phase: Apremilast 30 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and received 30 mg apremilast BID for an additional 52 weeks. Includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4.

| | |
|---|---|
| Subject analysis set title | Extension Phase Apremilast 40 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and received 40 mg apremilast BID for an additional 52 weeks. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase

## Primary: Percentage of Participants who Achieved a Clinical Remission by Total Mayo Score (TMS) at Week 12

| | |
|---|---|
| End point title | Percentage of Participants who Achieved a Clinical Remission by Total Mayo Score (TMS) at Week 12 |

End point description:

Clinical remission was defined as a total Mayo score ≤ 2 points, with no individual subscore exceeding 1 point. The TMS is an instrument designed to measure disease activity of UC. The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.

- Stool Frequency Subscore (SFS)
- Rectal Bleeding Subscore (RBS)
- Endoscopy Subscore
- Physician's Global Assessment (PGA).

Two-sided 95% confidence intervals (CI) for the within-group proportions are based on the Wilson score method. The intent to treat (ITT) population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| End point values | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 12.1 (6.0 to 22.9) | 31.6 (21.0 to 44.5) | 21.8 (12.9 to 34.4) | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.0142 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Differences in Percentages |
| Point estimate | 19.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.4 |
| upper limit | 33.6 |

Notes:

[1] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[2] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.2689 [4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified |
| Point estimate | 7.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 22.9 |

Notes:

[3] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method
[4] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants who Achieved a Clinical Response by Total Mayo Score and the Reduction in the Rectal Bleeding Subscore at Week 12

| End point title | Percentage of Participants who Achieved a Clinical Response by Total Mayo Score and the Reduction in the Rectal Bleeding Subscore at Week 12 |
|---|---|

End point description:

Clinical response was defined as a decrease from baseline in the TMS of at least 3 points and at least 30%, along with a reduction in the rectal bleeding subscore (RBS) of at least 1 point or an absolute RBS of ≤ 1. The TMS is an instrument designed to measure disease activity of UC. The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.

- Stool Frequency Subscore (SFS)
- Rectal Bleeding Subscore
- Endoscopy Subscore
- Physician's Global Assessment (PGA)

Rectal bleeding (subscore 0-3) was defined as:
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool
3 = Blood alone passes
Two-sided 95% CI for the within-group proportions are based on the Wilson score method.
The ITT population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Baseline to Week 12

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 46.6 (34.3 to 59.2) | 61.4 (48.4 to 72.9) | 67.3 (54.1 to 78.2) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[5] |
| P-value | = 0.1224 [6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 14.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 31.5 |

Notes:

[5] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[6] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.0401 [8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 19.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 36 |

Notes:

[7] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[8] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants who Achieved an Endoscopic Remission at Week 12

| End point title | Percentage of Participants who Achieved an Endoscopic Remission at Week 12 |
|---|---|

End point description:

An endoscopic remission was defined as a Mayo endoscopic subscore (MES) of 0 at Week 12.
The MES subscore findings were defined as:
0 = Normal or inactive disease
1 = Mild Disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration)

The endoscopy subscores consisted of findings that were centrally read through proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. Two-sided 95% CIs for the within-group percentage were based on the Wilson score method.
The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 3.4 (1.0 to 11.7) | 8.8 (3.8 to 18.9) | 7.3 (2.9 to 17.3) | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.2472 [10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 5.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.7 |
| upper limit | 16.7 |

Notes:

[9] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[10] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.4628 [12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 3.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 14.6 |

Notes:

[11] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[12] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants who Achieved an Endoscopic Response at Week 12

| End point title | Percentage of Participants who Achieved an Endoscopic Response at Week 12 |
|---|---|

End point description:

An endoscopic response is defined as a decrease from baseline of at least 1 point in the MES at Week

12. The Mayo endoscopy subscore findings were defined as:
0 = Normal or inactive disease
1 = Mild Disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration).

The endoscopy subscores consisted of findings that were centrally read through proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. Two-sided 95% CIs for the within-group percentage were based on the Wilson score method.
The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 41.4 (29.6 to 54.2) | 73.7 (61.0 to 83.4) | 47.3 (34.7 to 60.2) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.0005 [14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.8 |
| upper limit | 47.4 |

Notes:

[13] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[14] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |

| | |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.6878 [16] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.4 |
| upper limit | 21.5 |

Notes:

[15] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[16] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants Who Achieved a Rectal Bleeding Subscore (RBS) of ≤ 1 at Week 12

| | |
|---|---|
| End point title | Percentage of Participants Who Achieved a Rectal Bleeding Subscore (RBS) of ≤ 1 at Week 12 |

End point description:

The RBS was measured as:
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes

The daily bleeding score represents the most severe bleeding of the day. Two-sided 95% CI for the within-group proportions are based on the Wilson score method.
The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 72.4 (59.8 to 82.2) | 84.2 (72.6 to 91.5) | 87.3 (76.0 to 93.7) | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |

| | |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[17] |
| P-value | = 0.1388 [18] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 11.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | 26.1 |

Notes:

[17] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[18] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.0788 [20] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 13.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 27.7 |

Notes:

[19] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[20] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants Who Achieved Clinical Remission in the Modified Mayo Subscore (MMS) at Week 12

| End point title | Percentage of Participants Who Achieved Clinical Remission in the Modified Mayo Subscore (MMS) at Week 12 |
|---|---|

End point description:

Clinical remission was defined as a modified Mayo score of ≤ 2, with no individual subscore > 1, at Week 12. The MMS was based on a modification of the total Mayo score (TMS) which included the stool frequency, rectal bleeding, and endoscopic subscores of the TMS and excluded the Physician's Global Assessment (PGA) subscore, since this was a global measure that is subjective in nature. The MMS ranges from 0 to 9 points with higher scores indicating greater disease severity. The endoscopy subscores was centrally reviewed. Two-sided confidence intervals for the within-group percentage were based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| End point values | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 19.0 (10.9 to 30.9) | 43.9 (31.8 to 56.7) | 27.3 (17.3 to 40.2) | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.0046 [22] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 24.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.5 |
| upper limit | 40.1 |

Notes:

[21] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[22] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.4476 [24] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.8 |
| upper limit | 21.6 |

Notes:

[23] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[24] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants Who Achieved Clinical Response in the Modified Mayo Subscore (MMS) at Week 12

| End point title | Percentage of Participants Who Achieved Clinical Response in the Modified Mayo Subscore (MMS) at Week 12 |
|---|---|

End point description:

Clinical response in the MMS was defined as a decrease from baseline in the MMS of at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS ≤ 1. The MMS was based on the stool frequency, rectal bleeding, and endoscopic subscores of the TMS and excluded the PGA subscore. The MMS ranges from 0 to 9 points with higher scores indicating greater disease severity. The RBS was measured as: 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes. The daily bleeding score represents the most severe bleeding of the day. The endoscopy subscores was centrally reviewed. Two-sided confidence intervals for the within-group percentage were based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 12

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 46.6 (34.3 to 59.2) | 63.2 (50.2 to 74.5) | 67.3 (54.1 to 78.2) | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

| Comparison groups | Placebo v Apremilast 30 mg |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0755 [25] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified difference in proportions |
| Point estimate | 16.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 33.5 |

Notes:

[25] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | = 0.037 [27] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified difference in proportions |
| Point estimate | 19.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.5 |
| upper limit | 36.4 |

Notes:

[26] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[27] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants Who Achieved Clinical Remission in the Partial Mayo Subscore (PMS) With no Individual Subscore >1 at Week 8

| End point title | Percentage of Participants Who Achieved Clinical Remission in the Partial Mayo Subscore (PMS) With no Individual Subscore >1 at Week 8 |
|---|---|

End point description:

Clinical remission in the partial Mayo subscore was defined as a PMS of 2 points or lower, with no individual subscore >1. The PMS is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 9 (severe disease) and is a composite of 3 subscores:
Stool Frequency Subscore, Rectal Bleeding Subscore, and Physician's Global Assessment Subscore, each of which ranges from 0 (normal) to 3 (severe disease).
Two-sided 95% CI for the within-group proportions are based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:

Week 8

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 32.8 (22.1 to 45.6) | 47.4 (35.0 to 60.1) | 52.7 (39.8 to 65.3) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.1167 [29] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 14.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 31.4 |

Notes:

[28] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[29] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | = 0.0534 [31] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 18.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 34.9 |

Notes:

[30] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[31] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: Percentage of Participants Who Achieved Clinical Response in the Partial Mayo Subscore at Week 8

| End point title | Percentage of Participants Who Achieved Clinical Response in the Partial Mayo Subscore at Week 8 |
|---|---|

End point description:

Clinical response in the PMS was defined as a decrease from baseline in PMS of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. The PMS score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 9 (severe disease) and is a composite of 3 subscores:
Stool Frequency Subscore, Rectal Bleeding Subscore, and Physician's Global Assessment Subscore, each of which ranges from 0 (normal) to 3 (severe disease).
Two-sided 95% CI for the within-group proportions are based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

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

End point timeframe:
Week 8

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 48.3 (35.9 to 60.8) | 64.9 (51.9 to 76.0) | 81.8 (69.7 to 89.8) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Apremilast 30 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[32] |
| P-value | = 0.0758 [33] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 16.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 33.3 |

Notes:
[32] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[33] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo v Apremilast 40 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[34] |
| P-value | = 0.0004 [35] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Stratified Difference |
| Point estimate | 32.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.9 |
| upper limit | 47.5 |

Notes:

[34] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.
[35] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

## Secondary: The Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) During the Placebo-Controlled Phase

| End point title | The Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) During the Placebo-Controlled Phase |
|---|---|

End point description:

A TEAE was defined as any adverse event (AE) occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

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

End point timeframe:

From the first dose of investigational product (IP) and no later than 28 days after the last dose of IP for those who had completed the study or discontinued (D/C) early; maximum duration of exposure to treatment was 12.00 weeks

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: participants | | | | |
| Any TEAE | 31 | 28 | 36 | |
| Any IP-related TEAE | 12 | 13 | 20 | |
| Any Severe TEAE | 4 | 0 | 1 | |
| Any Serious TEAE | 2 | 0 | 1 | |
| Any Serious IP-related TEAE | 0 | 0 | 0 | |
| Any TEAE Leading to IP Withdrawal | 5 | 0 | 1 | |
| Any TEAE Leading to IP Interruption | 1 | 0 | 0 | |
| Any TEAE Leading to Death | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: The Number of Participants Who Discontinued Apremilast due to Treatment Emergent Adverse Events During the Placebo-Controlled Period

| End point title | The Number of Participants Who Discontinued Apremilast due to Treatment Emergent Adverse Events During the Placebo-Controlled Period |
|---|---|

End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and

up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

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

End point timeframe:

From the first dose of IP and no later than 28 days after the last dose of IP for those who had completed the study or discontinued early; median duration of exposure to treatment was 12.00 weeks

| **End point values** | Placebo | Apremilast 30 mg | Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 57 | 55 | |
| Units: participants | 5 | 0 | 2 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Number of Participants Who Experienced TEAEs During the Apremilast (APR) Exposure Period (Active Treatment Phase) Through Week 52

| End point title | The Number of Participants Who Experienced TEAEs During the Apremilast (APR) Exposure Period (Active Treatment Phase) Through Week 52 |
|---|---|

End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

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

End point timeframe:

From first dose of IP and no later than 28 days after last dose of IP for those who completed the active treatment phase or D/C early; median duration of exposure = 41.00, 44.15 and 40.00 weeks respectively for 30 mg, 40 mg and 30 mg/40 mg APR arms

| End point values | Apremilast 30 mg | Apremilast 40 mg | Apremilast 30 mg/Apremilast 40 mg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 83 | 80 | 11 | |
| Units: participants | | | | |
| Any TEAE | 60 | 67 | 8 | |
| Any Severe TEAE | 5 | 6 | 0 | |
| Any Serious TEAE | 6 | 8 | 1 | |
| Any TEAE Leading to Drug Withdrawal | 3 | 9 | 1 | |
| Any TEAE Leading to Drug Interruption | 1 | 4 | 0 | |
| Any TEAE Leading to Death | 0 | 0 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Number of Participants Who Experienced TEAEs During Week 52 to Week 104 (Extension Phase)

| End point title | The Number of Participants Who Experienced TEAEs During Week 52 to Week 104 (Extension Phase) |
|---|---|

End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain

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

End point timeframe:

From the first dose of IP at Week 52 and no later than 28 days after the last dose of IP for those who completed the study or had discontinued early; median exposure of apremilast for the total apremilast group was 52 weeks.

| End point values | Extension Phase: Apremilast 30 mg | Extension Phase Apremilast 40 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 45 | 54 | | |
| Units: participants | | | | |
| Any TEAE | 16 | 27 | | |
| Any Severe TEAE | 1 | 0 | | |
| Any Serious TEAE | 4 | 3 | | |
| Any Serious IP-related TEAE | 0 | 1 | | |
| Any TEAE Leading to IP Withdrawal | 2 | 1 | | |
| Any TEAE Leading to IP Interruption | 1 | 0 | | |
| Any TEAE Leading to Death | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events information

Timeframe for reporting adverse events:

From first dose of IP and no later than 28 days after the last dose of IP for those who had completed the study D/C early. AEs are reported for the placebo-controlled phase from Week 0 to Week 12 and for the APR exposure period from Week 0 to Week 104.

Adverse event reporting additional description:

Median duration of study drug was 12 weeks in the placebo controlled phase, 41.00, 44.15 and 40.00 weeks respectively for 30 mg, 40 mg and 30 mg/40 mg APR arms in the active treatment phase and 52 weeks in the extension phase; MedDRA Version 20.1 was used in the placebo controlled phase and Version 22 in the active treatment and extension phase.

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

## Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Placebo (Placebo Controlled Period) |

Reporting group description:

TEAEs for participants who were randomized to identically matching placebo capsules twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.

| | |
|---|---|
| Reporting group title | Apremilast 30 mg BID (Placebo Controlled Period) |

Reporting group description:

TEAEs for participants who were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

| | |
|---|---|
| Reporting group title | Apremilast 40 mg BID (Placebo Controlled Period) |

Reporting group description:

TEAEs for participants who were randomized to apremilast 40 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

| | |
|---|---|
| Reporting group title | Apremilast 30 mg BID (Apremilast Exposure Period) |

Reporting group description:

TEAEs during the apremilast 30 mg BID treatment for participants who received 30 mg apremilast capsules BID only and participants who initially received 30 mg apremilast capsules BID and switched to 40 mg apremilast capsules BID at Week 12, and participants who initially received placebo capsules BID and switched to 30 mg apremilast capsules BID at Week 12.

| | |
|---|---|
| Reporting group title | Apremilast 40 mg BID (Apremilast Exposure Period) |

Reporting group description:

TEAEs during the apremilast 40 mg BID treatment for participants who received 40 mg apremilast capsules BID only, and participants who initially received placebo BID and switched to 40 mg apremilast capsules BID at Week 12.

| | |
|---|---|
| Reporting group title | Apremilast 30/40 mg BID (Apremilast Exposure Period) |

Reporting group description:

TEAEs during the apremilast 40 mg BID treatment for participants who initially received 30 mg apremilast BID and switched to apremilast 40 mg BID at Week 12

| Serious adverse events | Placebo (Placebo Controlled Period) | Apremilast 30 mg BID (Placebo Controlled Period) | Apremilast 40 mg BID (Placebo Controlled Period) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from | 0 | 0 | 0 |

| adverse events | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Epididymal neoplasm | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epididymitis tuberculous | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Apremilast 30 mg BID (Apremilast Exposure Period) | Apremilast 40 mg BID (Apremilast Exposure Period) | Apremilast 30/40 mg BID (Apremilast Exposure Period) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 83 (10.84%) | 11 / 80 (13.75%) | 1 / 11 (9.09%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Epididymal neoplasm | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 3 / 80 (3.75%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 2 / 80 (2.50%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epididymitis tuberculous | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Placebo (Placebo Controlled Period) | Apremilast 30 mg BID (Placebo Controlled Period) | Apremilast 40 mg BID (Placebo Controlled Period) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 58 (34.48%) | 26 / 57 (45.61%) | 25 / 55 (45.45%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Angiomyolipoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Angiopathy | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 3 / 57 (5.26%) | 1 / 55 (1.82%) |
| occurrences (all) | 2 | 3 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 58 (3.45%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences (all) | 2 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 0 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 0 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 57 (3.51%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 2 | 1 |
| Investigations | | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Faecal calprotectin increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 12 / 57 (21.05%) | 14 / 55 (25.45%) |
| occurrences (all) | 10 | 17 | 20 |
| Migraine | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 1 | 2 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus headache | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 3 / 57 (5.26%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | 3 / 57 (5.26%) | 6 / 55 (10.91%) |
| occurrences (all) | 6 | 3 | 7 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 58 (3.45%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swollen tongue | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 2 / 57 (3.51%) | 2 / 55 (3.64%) |
| occurrences (all) | 1 | 2 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 3 / 55 (5.45%) |
| occurrences (all) | 1 | 0 | 3 |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 2 | 0 | 1 |
| Osteochondrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 4 / 57 (7.02%) | 2 / 55 (3.64%) |
| occurrences (all) | 2 | 4 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 0 | 1 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 2 / 57 (3.51%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 2 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Apremilast 30 mg BID (Apremilast Exposure Period) | Apremilast 40 mg BID (Apremilast Exposure Period) | Apremilast 30/40 mg BID (Apremilast Exposure Period) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 83 (59.04%) | 53 / 80 (66.25%) | 11 / 11 (100.00%) |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Angiomyolipoma | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Vascular disorders | | | |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 3 / 80 (3.75%) | 2 / 11 (18.18%) |
| occurrences (all) | 5 | 5 | 2 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 2 / 80 (2.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 2 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 2 / 80 (2.50%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 3 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 5 / 80 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 4 / 80 (5.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 80 (1.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 2 / 80 (2.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 2 | 1 |
| Investigations | | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Faecal calprotectin increased | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 1 / 80 (1.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 83 (20.48%) | 25 / 80 (31.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 25 | 35 | 2 |
| Migraine | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 3 / 80 (3.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 7 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 1 / 80 (1.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Sinus headache | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 3 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 4 / 80 (5.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 3 / 80 (3.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 3 | 1 |
| Nausea | | | |
| subjects affected / exposed | 8 / 83 (9.64%) | 9 / 80 (11.25%) | 3 / 11 (27.27%) |
| occurrences (all) | 8 | 10 | 4 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 2 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 6 / 80 (7.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 7 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 6 / 80 (7.50%) | 2 / 11 (18.18%) |
| occurrences (all) | 5 | 6 | 2 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 4 / 80 (5.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Swollen tongue | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 3 / 80 (3.75%) | 3 / 11 (27.27%) |
| occurrences (all) | 3 | 4 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 2 / 80 (2.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 2 | 1 |
| Pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 80 (2.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 1 / 80 (1.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 3 / 80 (3.75%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 6 / 80 (7.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 6 | 7 | 1 |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 83 (8.43%) | 8 / 80 (10.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 8 | 11 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 4 / 80 (5.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 3 / 80 (3.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 3 | 1 |
| Influenza | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 3 / 80 (3.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 4 | 1 |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | 1 / 80 (1.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 0 / 80 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 0 | 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 3 / 80 (3.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 3 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 80 (2.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 August 2014 | • The planned sample size was reduced from 249 to 165 after an internal decision to keep the Study CC-10004-UC-001 design in line with standard proof-of-concept Phase 2 trials.<br>• The assessment of the primary endpoint was changed from Week 8 to Week 12 because cumulative clinical experience in other indications suggests that apremilast may take a longer time to induce a clinical response than initially anticipated in the approved protocol. Clinical remission at Week 8 was planned to be evaluated as one of the key secondary endpoints.<br>• Secondary endpoints based on a modified Mayo score (without inclusion of PGA) were added based on a recommendation by the Food and Drug Administration during review of the original Investigational New Drug application.<br>• Nonresponder criteria were revised to allow patients with an incomplete response (partial responders) at Week 12 to continue blinded treatment, to assess the potential late response of apremilast in this population.<br>• Exclusion criterion 15 was added to clarify the psychiatric conditions that were exclusionary. |
| 13 April 2015 | • A treatment extension phase was added to provide all subjects the opportunity to receive active apremilast during the 40-week Blinded Active-treatment Phase.<br>• Concomitant medication restrictions were changed from a prohibition of background oral corticosteroid treatment to instead allow subjects to receive stable doses of prednisone ≤ 20 mg/day or equivalent or budesonide ≤ 9 mg/day.<br>• Stratification was added based on use of oral corticosteroids. Stratification based on use of aminosalicylates was deleted.<br>• The requirement for chest radiograph was removed.<br>• The psychiatric evaluation was updated based on feedback from the Health Authorities.<br>• Several efficacy-related exploratory endpoints were deleted and time points in the secondary and exploratory endpoints were modified due to the change in study duration.<br>• The definition of clinical remission based on the PMS was changed: "The proportion of subjects achieving clinical remission at Week 12, defined as a PMS of ≤ 2, with no individual subscore ≥ 1". Changed to > 1.<br>• The description in the sparse PK section was updated for clarity. |
| 20 July 2016 | • An Extension Phase was added for subjects who met the criteria for endoscopic response at Week 52 to allow these subjects to receive blinded, active treatment (apremilast) for an additional 52 weeks (Weeks 52 to 104).<br>• Safety information was updated to reflect the most recent version of the Investigator's Brochure.<br>• The following exploratory endpoints were added:<br>- The proportion of subjects with endoscopic remission, defined as a Mayo endoscopic subscore ≤ 1, and histological remission at Week 12<br>- The proportion of subjects achieving a clinical remission in the TMS at Week 12, defined as a TMS ≤ 2 with no individual subscore > 1 and no evidence of friability on the Mayo endoscopic subscore<br>- The exposure-adjusted incidence of UC-related health outcomes (eg, UC-related hospitalizations, emergency room visits, and surgeries) |

| | |
|---|---|
| 08 August 2018 | • The apremilast dose in the Extension Phase was adjusted so that all subjects participating in that phase of the study would receive apremilast 30 mg BID (rather than either apremilast 30 mg BID or 40 mg BID).<br>• Overdose for subjects receiving open-label 30 mg BID in the Extension Phase was defined as 4 or more 30-mg tablets in any 24-hour period (on a per-dose basis) or dosing more than 4 times in 24 hours (on a schedule or frequency basis).<br>• The DMC was decommissioned. After a meeting with the external DMC on 27 Oct 2017, Celgene determined that the DMC was no longer needed to support CC-10004-UC-001, as described in Section 6.<br>• Safety information was updated to reflect the most current information in the Investigator's Brochure.<br>• Clarification was added that subjects who experienced UC-related symptoms after corticosteroid tapering were permitted to receive the same treatment taken prior to tapering, provided that the dose was the same. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported