# Clinical trial results:
# A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis

## Summary

| | |
|---|---|
| EudraCT number | 2010-019992-30 |
| Trial protocol | AT ES DE DK IT |
| Global end of trial date | 30 November 2016 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 December 2017 |
| First version publication date | 17 December 2017 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CC-10004-PSOR-009 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01232283 |
| 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 | Weimin Wendy Zhang, Celgene Corporation, 01 908-514-9788, weizhang@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 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the clinical efficacy of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe plaque psoriasis.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 November 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 206 |
| Country: Number of subjects enrolled | Canada: 92 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | France: 22 |
| Country: Number of subjects enrolled | Germany: 52 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Spain: 17 |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Worldwide total number of subjects | 411 |
| EEA total number of subjects | 106 |

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) | 375 |
| From 65 to 84 years | 36 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 46 study centers in 9 countries.

### Pre-assignment

Screening details:

Subjects were eligible who had moderate to severe plaque psoriasis.

### Period 1

| | |
|---|---|
| Period 1 title | Placebo Controlled Phase (Weeks 0-16) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their week 52 visit

### Arms

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

Arm description:

Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16)

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16)

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16)

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

Dosage and administration details:

Placebo (identically-matching) tablets BID during the Placebo-controlled Phase (Weeks 0-16).

| Number of subjects in period 1 | Apremilast | Placebo |
|---|---|---|
| Started | 274 | 137 |
| Received apremilast | 272 | 136 |
| Completed | 239 | 112 |
| Not completed | 35 | 25 |
| Consent withdrawn by subject | 9 | 7 |
| Adverse event, non-fatal | 12 | 8 |
| Not specified | 2 | 1 |
| Noncompliance with study drug | 1 | - |
| Lost to follow-up | 6 | 6 |
| Lack of efficacy | 3 | 2 |
| Protocol deviation | 2 | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Maintenance Phase (Weeks 16-32) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their week 52 visit

## Arms

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

Arm description:

Participants who were initially randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16) remained on apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32).

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Maintenance Phase (Weeks 16-32)

| | |
|---|---|
| **Arm title** | Placebo-Apremilast |

Arm description:

Participants who were initially randomized to placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32)

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

| | |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | CC-10004 |
| Other name | Otzela |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg tablets BID during the Maintenance Phase (Weeks 16-32)

| **Number of subjects in period 2[1]** | Apremilast-Apremilast | Placebo-Apremilast |
|---|---|---|
| Started | 234 | 108 |
| Completed | 194 | 100 |
| Not completed | 40 | 8 |
| Consent withdrawn by subject | 7 | 1 |
| Adverse event, non-fatal | 8 | 2 |
| Non-compliance with study drug | 1 | - |
| Unspecified | 2 | - |
| Lost to follow-up | 3 | 2 |
| Lack of efficacy | 19 | 3 |

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: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 351 subjects who completed the Placebo-controlled Phase, 9 subjects withdrew from the study for diverse reasons including adverse events, protocol violations and withdrawal by subject. Consequently, a total of 342 subjects entered the Maintenance Phase of the trial.

## Period 3

| | |
|---|---|
| Period 3 title | Randomized Withdrawal Phase(Weeks 32-52) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their 52 week visit

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | APR-APR-Re-randomized to PBO |

Arm description:

Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a ≥PASI-50 response) were re-randomized to placebo during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who lost PASI-50 response achieved at Week 32, were switched back to apremilast 30 mg BID at the time the loss was observed. Those participants who did not lose at least 50% of the PASI response remained on placebo until Week 52. All participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and received apremilast 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Placebo (identically-matching) tablets BID during the Randomized Withdrawal Phase (Weeks 32-52).

| | |
|---|---|
| **Arm title** | APR-APR Re-randomized to APR |

Arm description:

Participants who were initially randomized to apremilast 30 mg tablets BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a ≥PASI-50 response) were re-randomized to apremilast during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on APR 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

| | |
|---|---|
| **Arm title** | APR-APR-APR + optional topicals/phototherapy |

Arm description:

Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At Week 32, those participants who were considered non-responders (ie, having a response of <PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topicals or phototherapy. Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

| | |
|---|---|
| **Arm title** | PBO-APR-APR + optional topicals/phototherapy |

Arm description:

Participants who were initially randomized to placebo BID during the 16-week Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32). At week 32, all participants were to maintain apremilast 30 mg BID; those who were non-responders (having a response of <PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topical or phototherapy. All participants who completed the Randomized Withdrawal Phase at week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation.

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

| | |
|---|---|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | CC-10004 |
| Other name | Otzela |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

| **Number of subjects in period 3[2]** | APR-APR-Re-randomized to PBO | APR-APR Re-randomized to APR | APR-APR-APR + optional topicals/phototherapy |
|---|---|---|---|
| Started | 62 | 61 | 58 |
| Treated with APR+ topicals/phototherapy | 0 [3] | 0 [4] | 28 [5] |
| Completed | 50 | 56 | 41 |
| Not completed | 12 | 5 | 17 |
| Adverse event, serious fatal | 1 | - | - |
| Consent withdrawn by subject | 3 | 3 | 3 |
| Adverse event, non-fatal | 2 | 1 | - |
| Unspecified | - | 1 | - |
| Lost to follow-up | 2 | - | 1 |
| Lack of efficacy | 4 | - | 13 |
| Protocol deviation | - | - | - |

| **Number of subjects in period 3[2]** | PBO-APR-APR + optional topicals/phototherapy |
|---|---|
| Started | 96 |
| Treated with APR+ topicals/phototherapy | 17 [6] |
| Completed | 84 |
| Not completed | 12 |
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | 4 |
| Adverse event, non-fatal | 1 |
| Unspecified | - |
| Lost to follow-up | 1 |
| Lack of efficacy | 5 |
| Protocol deviation | 1 |

Notes:

[2] - 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: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 294 subjects who completed the Maintenance Phase, 17 subjects withdrew from the study

for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 277 subjects entered the Randomized Withdrawal Phase of the trial.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Of the 123 subjects who were originally randomized to APR and who achieved a PASI-75 response at Week 32, 62 subjects were re-randomized to placebo and 50 subjects in this group completed the Randomized Withdrawal Phase. Subjects in this treatment group were not permitted to receive topical and/or phototherapy during the Randomization Withdrawal Phase.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Of the 123 subjects who were originally randomized to APR and who achieved a PASI-75 response at Week 32, 61 subjects were re-randomized to APR and 56 subjects in this group completed the Randomized Withdrawal Phase. Subjects in this treatment group were not permitted to receive topical and/or phototherapy during the Randomization Withdrawal Phase.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Of the 194 subjects who were originally randomized to APR and completed the Maintenance Phase, 13 withdrew from the study for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 181 subjects entered the Randomized Withdrawal Phase. Among them, 123 subjects were re-randomized (62 to PBO, 61 to APR) and 58 subjects entered this arm. Of the 58 subjects, 28 were treated with topicals and/or phototherapy, and 30 did not receive topical and/or phototherapy
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Of the 100 subjects who were originally randomized to PBO, switched to APR and completed the Maintenance Phase with APR, 4 subjects withdrew from the study for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 96 subjects entered the Randomization Withdrawal Phase of the trial. Of the 96 subjects in the PBO-APR-APR arm, 17 subjects were treated with topical therapy and/or phototherapy, and 79 subjects did not receive topical and/or phototherapy.

## Period 4

| | |
|---|---|
| Period 4 title | Long-Term Extension Phase (Weeks 52-260) |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Apremilast (Long-Term Extension Phase) |

Arm description:

Participants who were initially randomized to APR 30 mg BID during the 16-week placebo-controlled phase (Weeks 0-16) continued receiving APR 30 mg BID through the Maintenance Phase (weeks 16-32) and apremilast 30 mg tablets or placebo during the Randomized Withdrawal Phase were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and remained on APR 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Long-Term Extension Phase (Weeks 52-260)

| | |
|---|---|
| **Arm title** | Placebo-Apremilast (Long-term extension) |

Arm description:

Participants who were initially randomized to identically matching placebo BID during the Placebo-controlled Phase (Weeks 0-16) were switched at Week 16 to apremilast 30 mg BID during the

Maintenance Phase, received apremilast 30 mg PO BID during the Randomized Withdrawal Phase and then continued to receive apremilast 30 mg tablets BID in the long-term extension phase from weeks 52-260.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Long-term Extension Phase (Weeks 50-260)

| **Number of subjects in period 4[7]** | Apremilast (Long-Term Extension Phase) | Placebo-Apremilast (Long-term extension) |
|---|---|---|
| Started | 137 | 80 |
| Completed | 29 | 19 |
| Not completed | 108 | 61 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 30 | 14 |
| Adverse event, non-fatal | 11 | 6 |
| Miscellaneous | 7 | 3 |
| Non-compliance | 3 | 2 |
| Lost to follow-up | 9 | 6 |
| Lack of efficacy | 46 | 30 |
| Protocol deviation | 1 | - |

Notes:

[7] - 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: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 231 subjects who completed the Randomized Withdrawal Phase, 14 subjects withdrew from the study for diverse reasons including adverse events, lack of efficacy, non-compliance and withdrawal by subject. Consequently, a total of 217 subjects entered the Long-Term Extension of the trial.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Apremilast |
| Reporting group description: | |
| Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16) | |

| Reporting group values | Apremilast | Placebo | Total |
|---|---|---|---|
| Number of subjects | 274 | 137 | 411 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 252 | 123 | 375 |
| From 65-84 years | 22 | 14 | 36 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 45.3 | 45.7 | |
| standard deviation | ± 13.05 | ± 13.38 | - |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 98 | 37 | 135 |
| Male | 176 | 100 | 276 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 8 | 6 | 14 |
| Black or African American | 13 | 2 | 15 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| White | 250 | 128 | 378 |
| Other-not specified | 1 | 0 | 1 |
| Study Specific Characteristic \| Duration of Plaque Psoriasis | | | |
| All participants enrolled were required to have a diagnosis of plaque psoriasis at least 12 months prior to screening, but the duration was not required for enrollment. Overall baseline population for duration of plaque psoriasis in the apremilast arm were 271 participants and 135 for those in the placebo arm. | | | |
| Units: years | | | |
| arithmetic mean | 17.94 | 18.68 | |

| | | | |
|---|---|---|---|
| standard deviation | ± 11.367 | ± 12.088 | - |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | APR: Subjects with TEAEs during the APR-Exposure Phase |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for participants originally randomized to placebo) to the last dose of apremilast. Adverse events that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose.

| | |
|---|---|
| Subject analysis set title | APR: Subjects with Psoriasis Flare in the APR-Exposure Phase |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI >= 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2].

| **Reporting group values** | APR: Subjects with TEAEs during the APR-Exposure Phase | APR: Subjects with Psoriasis Flare in the APR-Exposure Phase | |
|---|---|---|---|
| Number of subjects | 380 | 380 | |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 45.3 | 45.7 | |
| standard deviation | ± 13.05 | ± 13.38 | |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female<br>Male | | | |

| | | | |
|---|---|---|---|
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native<br>Asian<br>Black or African American<br>Native Hawaiian or Other Pacific Islander<br>White<br>Other-not specified | | | |
| Study Specific Characteristic \| Duration of Plaque Psoriasis | | | |
| All participants enrolled were required to have a diagnosis of plaque psoriasis at least 12 months prior to screening, but the duration was not required for enrollment. Overall baseline population for duration of plaque psoriasis in the apremilast arm were 271 participants and 135 for those in the placebo arm. | | | |
| Units: years | | | |
| arithmetic mean | 17.94 | 18.68 | |
| standard deviation | ± 11.37 | ± 12.088 | |

## End points

### End points reporting groups

| Reporting group title | Apremilast |
|---|---|
| Reporting group description: | |
| Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16) | |
| Reporting group title | Apremilast-Apremilast |
| Reporting group description: | |
| Participants who were initially randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16) remained on apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32). | |
| Reporting group title | Placebo-Apremilast |
| Reporting group description: | |
| Participants who were initially randomized to placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32) | |
| Reporting group title | APR-APR-Re-randomized to PBO |
| Reporting group description: | |
| Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a ≥PASI-50 response) were re-randomized to placebo during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who lost PASI-50 response achieved at Week 32, were switched back to apremilast 30 mg BID at the time the loss was observed. Those participants who did not lose at least 50% of the PASI response remained on placebo until Week 52. All participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and received apremilast 30 mg BID for the remainder of their participation. | |
| Reporting group title | APR-APR Re-randomized to APR |
| Reporting group description: | |
| Participants who were initially randomized to apremilast 30 mg tablets BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a ≥PASI-50 response) were re-randomized to apremilast during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on APR 30 mg BID for the remainder of their participation. | |
| Reporting group title | APR-APR-APR + optional topicals/phototherapy |
| Reporting group description: | |
| Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At Week 32, those participants who were considered non-responders (ie, having a response of <PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topicals or phototherapy. Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation. | |
| Reporting group title | PBO-APR-APR + optional topicals/phototherapy |
| Reporting group description: | |
| Participants who were initially randomized to placebo BID during the 16-week Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32). At week 32, all participants were to maintain apremilast 30 mg BID; those who were non-responders (having a response of <PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topical or phototherapy. All participants who completed the Randomized Withdrawal Phase at week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast | |

30 mg BID for the remainder of their participation.

| Reporting group title | Apremilast (Long-Term Extension Phase) |
|---|---|

Reporting group description:

Participants who were initially randomized to APR 30 mg BID during the 16-week placebo-controlled phase (Weeks 0-16) continued receiving APR 30 mg BID through the Maintenance Phase (weeks 16-32) and apremilast 30 mg tablets or placebo during the Randomized Withdrawal Phase were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and remained on APR 30 mg BID for the remainder of their participation.

| Reporting group title | Placebo-Apremilast (Long-term extension) |
|---|---|

Reporting group description:

Participants who were initially randomized to identically matching placebo BID during the Placebo-controlled Phase (Weeks 0-16) were switched at Week 16 to apremilast 30 mg BID during the Maintenance Phase, received apremilast 30 mg PO BID during the Randomized Withdrawal Phase and then continued to receive apremilast 30 mg tablets BID in the long-term extension phase from weeks 52-260.

| Subject analysis set title | APR: Subjects with TEAEs during the APR-Exposure Phase |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for participants originally randomized to placebo) to the last dose of apremilast. Adverse events that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose.

| Subject analysis set title | APR: Subjects with Psoriasis Flare in the APR-Exposure Phase |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI >= 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2].

## Primary: Percentage of participants Who Achieved at least a 75% improvement (response) in the Psoriasis Area Severity Index (PASI-75) at Week 16 from Baseline

| End point title | Percentage of participants Who Achieved at least a 75% improvement (response) in the Psoriasis Area Severity Index (PASI-75) at Week 16 from Baseline |
|---|---|

End point description:

PASI-75 response is the percentage of subjects who achieved at least a 75% reduction (improvement) from baseline in PASI score at week 16. The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). Full Analysis Set (FAS) consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group in which they were randomized. Last observation carried forward.

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

End point timeframe:

Baseline to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 137 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 28.8 | 5.8 | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.3 |
| upper limit | 29.6 |

**Secondary: Percentage of Participants who Achieved a Static Physician Global Assessment (sPGA) Score of Clear (0) or Almost Clear (1) with at Least 2 Points Reduction from Baseline**

| End point title | Percentage of Participants who Achieved a Static Physician Global Assessment (sPGA) Score of Clear (0) or Almost Clear (1) with at Least 2 Points Reduction from Baseline |
|---|---|

End point description:

The sPGA was a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall severity, the Investigator must have factored in areas that have already been cleared (ie, have scores of 0) and not just evaluate remaining lesions for severity, ie, the severity of each sign was averaged across all areas of involvement, including cleared lesions. In the event of different severities across disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

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

End point timeframe:

Baseline to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 137 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 20.4 | 4.4 | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 16.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.2 |
| upper limit | 21.9 |

**Secondary: Percent Change from Baseline in the Affected Body Surface Area (BSA) at Week 16**

| End point title | Percent Change from Baseline in the Affected Body Surface Area (BSA) at Week 16 |
|---|---|

End point description:

BSA was a measurement of involved skin. The overall BSA affected by psoriasis was estimated based on the palm area of the participant's hand (entire palmar surface or "handprint" including the fingers), which equates to approximately 1% of total body surface area. BSA percent change from baseline (Visit 2 Week 0) was determined at each visit of the study, which is calculated as 100*(visit BSA – baseline BSA) / baseline BSA (%). The Full Analysis Set (FAS) consisted of all participants who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. Subjects with a baseline value and at least 1 post-baseline value were included. LOCF imputation was used.

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

End point timeframe:

Baseline and Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 269 | 136 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -48.40 (± 2.636) | -6.25 (± 3.710) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Mean |
| Point estimate | -42.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.11 |
| upper limit | -33.2 |

Notes:

[1] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

**Secondary: Percent Change from Baseline in the Psoriasis Area Severity Index (PASI) score at Week 16**

| End point title | Percent Change from Baseline in the Psoriasis Area Severity Index (PASI) score at Week 16 |
|---|---|

End point description:

PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used. Subjects with a baseline value and at least 1 post-baseline value are included.

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

End point timeframe:

Baseline and Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 269 | 136 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -50.8 (± 2.23) | -16.0 (± 3.15) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -34.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.4 |
| upper limit | -27.2 |

Notes:

[2] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

**Secondary: Percentage of Participants Who Achieved a 50% Improvement (response) in the PASI Score (PASI-50) at Week 16 from Baseline**

| End point title | Percentage of Participants Who Achieved a 50% Improvement (response) in the PASI Score (PASI-50) at Week 16 from Baseline |
|---|---|

End point description:

PASI-50 response is the percentage of participants who achieved at least a 50% reduction (improvement) from baseline in PASI score at Week 16. The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

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

End point timeframe:

Baseline and Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 137 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 55.5 | 19.7 | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 35.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 26.9 |
| upper limit | 44.7 |

**Secondary: Change from Baseline in Pruritus Visual Analog Scale (VAS) Score at Week 16**

| End point title | Change from Baseline in Pruritus Visual Analog Scale (VAS) Score at Week 16 |
|---|---|

End point description:

The Pruritus Visual Analog Scores (VAS) were used to measure the amount of itching and discomfort a participant experiences. Subject's assessment of Pruritus (Itch) asked: On average, how much itch have you had because of your condition in the past week? All VAS values range from 0 to 100. Higher scores correspond to more severe symptom or disease. Change from baseline was calculated for the VAS scale, where change = visit value − baseline value. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used. Subjects with a baseline value and at least 1 post-baseline value are included.

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

End point timeframe:

Baseline and Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 133 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -33.5 (± 2.08) | -12.2 (± 2.95) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -21.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.4 |
| upper limit | -14.2 |

Notes:

[3] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

**Secondary: Change from Baseline in Dermatology Life Quality Index (DLQI) total score at Week 16**

| End point title | Change from Baseline in Dermatology Life Quality Index (DLQI) total score at Week 16 |
|---|---|

End point description:

DLQI is a practical questionnaire to assess limitations related to the impact of skin disease. DLQI contains 10 items dealing with the subject's skin. With the exception of Item Number 7, the subject responds on a 4-point scale, ranging from "Very Much" (score 3) to "Not at All" or "Not relevant" (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the subjects skin prevented them from working or studying, and if "No," then the subject is asked how much of a problem the skin has been at work or study over the past week, with responses being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score was derived by summing all item scores, having a range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 to the best. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized for the FAS. LOCF imputation was used.

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

End point timeframe:

Baseline and Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267 | 131 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -6.7 (± 0.37) | -2.7 (± 0.53) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.3 |
| upper limit | -2.8 |

Notes:

[4] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

**Secondary: Change from Baseline in the Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 at Week 16**

| End point title | Change from Baseline in the Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 at Week 16 |
|---|---|

End point description:

The SF-36 was a health instrument consisting of 8 scales: physical function, role limitations–physical, vitality, general health perceptions, bodily pain, social function, role limitations–emotional and mental health. Scale scores range from 0 to 100, with higher scores indicating better health. 2 overall summary scores were obtained − a Physical Component Summary score (PCS) and a Mental Component Summary (MCS) score. Scores from the 8 scales, PCS and MCS were transformed to the norm-based scores using weights from U.S. general population, with 50 as the average and 10 as the standard deviation, higher scores indicating better health. For norm based scores, change from baseline were calculated for the 8 scales and the two summary scales, where change = visit value − baseline value. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized. LOCF imputation was used.

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

End point timeframe:

Baseline to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267 | 131 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 2.60 (± 0.563) | -0.03 (± 0.804) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.0078 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 4.56 |

Notes:

[5] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate

**Secondary: Percentage of Participants Who Achieved Both a 75% Improvement (response) in the PASI and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction at Week 16 from Baseline**

| End point title | Percentage of Participants Who Achieved Both a 75% Improvement (response) in the PASI and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction at Week 16 from Baseline |
|---|---|

End point description:

PASI-75 response is the percentage of participants who achieved at least a 75% reduction (improvement) from baseline in PASI score at Week 16. The improvement in PASI score was used as a measure of efficacy. See Outcome measure #1 for further description. sPGA is a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. See Outcome Measure #2 for further description. The Full Analysis Set (FAS) consisted of all participants who were randomized per protocol. Participants were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

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

End point timeframe:

Baseline to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 137 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 18.6 | 4.4 | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Apremilast v Placebo |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 14.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.5 |
| upper limit | 20 |

**Secondary: Time to Loss of Effect (loss of 50% improvement in PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase**

| End point title | Time to Loss of Effect (loss of 50% improvement in PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase |
|---|---|

End point description:

Time to loss was the time between the re-randomization date and the date of the first assessment with loss of 50% PASI improvement (event), or the time between the re-randomization date and the date of the last PASI assessment in the randomized withdrawal phase prior to addition of topical/phototherapy or other effective psoriasis therapies, or resumption of apremilast 30 mg BID, or discontinuation, or Week 52 if no loss (censored), whichever was earlier. Analysis population consisted of participants who were re-randomized to placebo or Apremilast 30mg BID at Week 32.

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

End point timeframe:

Weeks 32 to Week 52

| End point values | APR-APR-Re-randomized to PBO | APR-APR Re-randomized to APR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 61 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 12.4 (8.3 to 20.1) | 21.9 (-99999 to 99999) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | APR-APR-Re-randomized to PBO v APR-APR Re-randomized to APR |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 7.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.408 |
| upper limit | 17.399 |

**Secondary: Number of Participants with Adverse Events (AE) in the Placebo Controlled Phase**

| End point title | Number of Participants with Adverse Events (AE) in the Placebo Controlled Phase |
|---|---|

End point description:

An AE was any noxious, unintended, or untoward medical occurrence, that may worsen in a subject during the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values regardless of cause. Any worsening (ie.,clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE is any untoward AE that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly/birth defect, or is a condition that may jeopardize the patient or require intervention to prevent one of the outcomes above. An AE is a treatment emergent if the AE start date is on or after the date of the lst dose of IP and no later than 28 days after the last dose. Safety population = subjects randomized and received at least 1 dose of IP.

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

End point timeframe:

Baseline to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 272 | 136 | | |
| Units: participants | | | | |
| Any TEAE | 185 | 82 | | |
| Any drug related TEAE | 106 | 29 | | |
| Any Severe TEAE | 12 | 6 | | |
| Any Serious TEAE | 5 | 3 | | |
| Any TEAE leading to drug interruption | 16 | 4 | | |
| Any TEAE leading to drug withdrawal | 15 | 7 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Psoriasis Flare or Rebound in the Placebo Controlled Phase

| End point title | Number of Participants with Psoriasis Flare or Rebound in the Placebo Controlled Phase |
|---|---|

End point description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. PASI >= 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2]. Safety population consisted of all subjects who were randomized and received at least one dose of IP

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

End point timeframe:

Week 0 to Week 16

| End point values | Apremilast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 272 | 136 | | |
| Units: participants | | | | |
| Participants with any psoriasis flare [1] | 3 | 7 | | |
| Participants with any psoriasis rebound [2] | 1 | 0 | | |
| PASI ≥ 125% of Baseline score after last dose [3] | 1 | 2 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with TEAEs During the Apremilast-Exposure Period Through Week 260

| End point title | Number of Participants with TEAEs During the Apremilast-Exposure Period Through Week 260 |
|---|---|

End point description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for subjects originally randomized to placebo) to the last dose of apremilast. AEs that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose. Apremilast subjects as treated.

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

End point timeframe:

Week 0 to Week 260; The mean duration of exposure was 100.66 weeks.

| **End point values** | APR: Subjects with TEAEs during the APR-Exposure Phase | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 380 | | | |
| Units: participants | | | | |
| Any TEAE | 316 | | | |
| Any Drug-Related TEAE | 165 | | | |
| Any Severe TEAE | 58 | | | |
| Any Serious TEAE | 44 | | | |
| Any Serious Drug-Related TEAE | 8 | | | |
| Any TEAE Leading to Drug Interruption | 56 | | | |
| Any TEAE Leading to Drug Withdrawal | 45 | | | |
| Any TEAE Leading to Death | 1 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Psoriasis Flare or Rebound in the Apremilast-Exposure Period

| End point title | Number of Participants with Psoriasis Flare or Rebound in the Apremilast-Exposure Period |
|---|---|

End point description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis,

Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI >= 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2]. The apremilast subjects as treated population.

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

End point timeframe:

Week 0 to Week 260

| **End point values** | APR: Subjects with Psoriasis Flare in the APR-Exposure Phase | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 380 | | | |
| Units: participants | | | | |
| Participants with any psoriasis flare [1] | 25 | | | |
| Participants with any psoriasis rebound [2] | 11 | | | |
| PASI ≥ 125% of Baseline score after last dose [3] | 12 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events information

Timeframe for reporting adverse events:

AEs are reported at: 1. Weeks 0-16: PBO-controlled phase 2. Weeks 32-52 Randomized Withdrawal participants re-randomized to PBO at Week 32 3. Weeks 0-260 APR-exposure period for participants randomized or switched to APR at any time during the study

Adverse event reporting additional description:

During the PBO-controlled Phase (Weeks 0-16), the mean duration of treatment for those randomized to APR 30 BID or PBO at Week 0, was 14.0 and 14.6, respectively; for those re-randomized to PBO at Week 32, the mean duration of PBO was 11.6 weeks; during the APR-Exposure Period (Weeks 0-260), the mean duration of exposure to APR was 100.66 weeks

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

## Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Placebo: Weeks 0-16 (PBO-Controlled Phase) |

Reporting group description:

Participants randomized to identically matching placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16)

| | |
|---|---|
| Reporting group title | APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase) |

Reporting group description:

Participants re-randomized to placebo tablets BID at Week 32. Includes data from Week 32 up to Week 52 when participants received placebo treatment.

| | |
|---|---|
| Reporting group title | Apremilast: Weeks 0-260 (APR-Exposure Period) |

Reporting group description:

Participants who received apremilast 30 mg tablets BID, regardless of when the apremilast exposure started (at Week 0 or at Week 16), up until Week 260. Adverse events associated with apremilast 30 mg treatment up to Week 260 were included. AEs that started more than 28 days after Placebo treatment and prior to resuming apremilast were excluded for participants who were re-randomized to Placebo at Week 32

| | |
|---|---|
| Reporting group title | Apremilast: Weeks 0-16 (PBO-Controlled Phase) |

Reporting group description:

Participants randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16)

| Serious adverse events | Placebo: Weeks 0-16 (PBO-Controlled Phase) | APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase) | Apremilast: Weeks 0-260 (APR-Exposure Period) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 136 (2.21%) | 2 / 62 (3.23%) | 44 / 380 (11.58%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| 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 | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Personality disorder | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Helicobacter test positive | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Palpitations | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 62 (0.00%) | 0 / 380 (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 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia paroxysmal | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 62 (1.61%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 62 (1.61%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Angle closure glaucoma | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Maculopathy | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 2 / 380 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pustular psoriasis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 2 / 380 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriatic arthropathy | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Appendicitis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 2 / 380 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 62 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Apremilast: Weeks 0-16 (PBO-Controlled Phase) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 272 (1.84%) | | |
| number of deaths (all causes) | 0 | | |

| | | | |
|---|---|---|---|
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Personality disorder | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Helicobacter test positive | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palpitations | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachyarrhythmia | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia paroxysmal | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parkinson's disease | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subarachnoid haemorrhage | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Syncope | | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Maculopathy | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Psoriasis | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pustular psoriasis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gouty arthritis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psoriatic arthropathy | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 272 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |
| subjects affected / exposed | 1 / 272 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Placebo: Weeks 0-16 (PBO-Controlled Phase) | APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase) | Apremilast: Weeks 0-260 (APR-Exposure Period) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 136 (27.94%) | 17 / 62 (27.42%) | 234 / 380 (61.58%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 62 (0.00%) | 28 / 380 (7.37%) |
| occurrences (all) | 1 | 0 | 52 |
| Tension headache | | | |
| subjects affected / exposed | 2 / 136 (1.47%) | 0 / 62 (0.00%) | 31 / 380 (8.16%) |
| occurrences (all) | 2 | 0 | 52 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 136 (5.88%) | 1 / 62 (1.61%) | 62 / 380 (16.32%) |
| occurrences (all) | 9 | 1 | 96 |
| Nausea | | | |
| subjects affected / exposed | 9 / 136 (6.62%) | 2 / 62 (3.23%) | 68 / 380 (17.89%) |
| occurrences (all) | 10 | 2 | 91 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 136 (3.68%) | 0 / 62 (0.00%) | 27 / 380 (7.11%) |
| occurrences (all) | 7 | 0 | 30 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 7 / 136 (5.15%) | 1 / 62 (1.61%) | 24 / 380 (6.32%) |
| occurrences (all) | 7 | 1 | 37 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 136 (1.47%) | 2 / 62 (3.23%) | 26 / 380 (6.84%) |
| occurrences (all) | 2 | 3 | 30 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 136 (1.47%) | 2 / 62 (3.23%) | 31 / 380 (8.16%) |
| occurrences (all) | 2 | 2 | 42 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 136 (1.47%) | 1 / 62 (1.61%) | 19 / 380 (5.00%) |
| occurrences (all) | 3 | 1 | 19 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 62 (1.61%) | 29 / 380 (7.63%) |
| occurrences (all) | 0 | 1 | 39 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 136 (4.41%) | 5 / 62 (8.06%) | 69 / 380 (18.16%) |
| occurrences (all) | 7 | 6 | 118 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 136 (4.41%) | 1 / 62 (1.61%) | 53 / 380 (13.95%) |
| occurrences (all) | 6 | 1 | 76 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 62 (1.61%) | 22 / 380 (5.79%) |
| occurrences (all) | 0 | 1 | 26 |

| **Non-serious adverse events** | Apremilast: Weeks 0-16 (PBO-Controlled Phase) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 128 / 272 (47.06%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 272 (6.25%) | | |
| occurrences (all) | 35 | | |
| Tension headache | | | |
| subjects affected / exposed | 20 / 272 (7.35%) | | |
| occurrences (all) | 25 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 43 / 272 (15.81%) | | |
| occurrences (all) | 54 | | |
| Nausea | | | |
| subjects affected / exposed | 50 / 272 (18.38%) | | |
| occurrences (all) | 61 | | |

| | | | |
|---|---|---|---|
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 14 / 272 (5.15%)<br>15 | | |
| Skin and subcutaneous tissue disorders<br>Psoriasis<br>subjects affected / exposed<br>occurrences (all) | 3 / 272 (1.10%)<br>3 | | |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 5 / 272 (1.84%)<br>5<br>6 / 272 (2.21%)<br>11<br>6 / 272 (2.21%)<br>6 | | |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 272 (1.47%)<br>4<br>20 / 272 (7.35%)<br>28<br>13 / 272 (4.78%)<br>13<br>5 / 272 (1.84%)<br>6 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 January 2011 | 1. Clarified procedures for subjects who entered the Randomized Treatment Withdrawal Phase at Week 32 2. Clarified that Arthritis VAS only pertained to subjects with psoriatic arthritis 3. Clarified the language regarding contraception methods to ensure that acceptable methods of contraception by subjects were used and added a statement to ensure that appropriate education regarding contraception methods was provided by the investigator to the subjects 4. Limited sites to North America and Europe 5. Corrected the order of health-related quality of life (HRQoL) and VAS assessments to align with what is actually being done on the SitePad instrument 6. Aligned exclusion criteria related to past malignancies across the entire apremilast Phase 3 program in order to give investigators responsibility for determining subject eligibility for previously successfully treated local lesions 7. Clarified Statistical Efficacy Analysis deleting the "Per-protocol" analysis 8. Modified the Reasons for Discontinuation to align with what is displayed in the InForm database |
| 10 June 2011 | 1. Provided updates to the contact information for the medical monitor of the study 2. Provide correction regarding the Celgene Therapeutic Area Head of the study 3. Clarified the Contraception Education that required the investigator to educate the subject on acceptable birth control any time when a subject's contraceptive measures or ability to become pregnant changed; modified to direct the investigator to Section 7.2 of the protocol where details regarding the acceptable contraception for this study may be found 4. Modified Inclusion Criterion Number 9 (female birth control) to clearly define single or multiple forms of contraception that were acceptable for this study 5. Added a footnote to Inclusion Criterion Number 9 (female birth control) to clarify that the female subject's chosen form of contraception must be fully effective by the time the female subject is randomized into the study 6. Modified Inclusion Criterion Number 10 (male birth control) to clarify that male subjects must use a "male" latex or non-latex condom 7. Deleted descriptive text on how to record onset and end dates of SAEs on the SAE Report Form because it is no longer applicable |
| 19 April 2012 | 1. Provided updates to the contact information for the medical monitor of the study 2. Clarified Section 3.2.2, Efficacy, and in Section 3.3, Exploratory Endpoint(s), that the VAS scale endpoints were to be change from baseline rather than percent change 3. Modified Section 4.1, Study Design, to allow the use of topical corticosteroids, retinoids or vitamin D analog preparations and/or phototherapy after the Week 52 study visit for non-responders 4. Modified Section 4.1, Study Design, regarding the replacement of the Safety Review Panel with an independent external DMC 5. Added footnotes to the Tables of Events clarifying that vasculitis assessments and/or psychiatric evaluations were to be performed as appropriate when adverse events were reported 6. Revised the Contraception Education language in Section 6.2 and moved footnote from Section 7.2 to Section 6.2 7. Added Section 6.6.4.1, Vasculitis Assessment, providing guidance to investigators 8. Added Section 6.6.4.2, Psychiatric Evaluation, to provide precautionary guidance to investigators for the management of subjects identified as having thoughts of suicide, attempted suicide or having major psychiatric illness 9. Added open-label IP package description in Section 6.10.1, Investigational Product Dispensing and Counting for Compliance, and Section 8.4, Packaging and Labeling 10. Modified Section 9.1, Permitted Concomitant Medications, and Section 9.2, Prohibited Concomitant Medications, to allow the use of topical corticosteroids, retinoids, or vitamin D analog preparations and/or phototherapy after the Week 52 study visit for non-responders 11. Clarified that AE tables were to summarize treatment-emergent AE only 12. Changed "CRF" to "eCRF" globally throughout the document, to reflect that data captured in this study in electronic case report form pages (eCRF) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported