



Clinical trial results:

A Phase 4, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in Subjects With Early, Oligoarticular Psoriatic Arthritis Despite Initial Stable Treatment With Either NSAIDs and/or 1 Conventional Synthetic DMARD

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2018-002735-26 |
| Trial protocol | DE FR ES BE NL GB IT |
| Global end of trial date | 05 July 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 05 May 2024 |
| First version publication date | 05 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | CC-10004-PSA-013 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03747939 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, |
| Public contact | Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 | 05 July 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 July 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of apremilast 30 mg BID with or without NSAIDs and/or csDMARDs versus placebo with or without NSAIDs and/or csDMARDs in subjects with early oligoarticular psoriatic arthritis (PsA), assessed by modified MDA-Joints.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation Good Clinical Practice regulations/guidelines and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 31 December 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Italy: 28 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | United States: 163 |
| Country: Number of subjects enrolled | Russian Federation: 66 |
| Worldwide total number of subjects | 308 |
| EEA total number of subjects | 55 |

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) | 259 |
| From 65 to 84 years | 49 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 80 study centers in Austria, Belgium, Canada, France, Germany, Italy, Spain, the United Kingdom, and the United States from 31 December 2018 to the last participant's last study visit on 05 July 2023. Of the 310 enrolled participants, 2 were enrolled in error and did not receive any dose of investigational product.

Pre-assignment

Screening details:

Participants with PsA were randomized in a 2:1 ratio to receive apremilast or placebo. At week 16, participants with no swollen joint count (SJC) improvement could have escaped early to receive apremilast 30 mg twice daily (BID). At week 24, eligible participants entered the extension phase to receive apremilast 30 mg BID up to week 48.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Placebo-controlled Phase (Weeks 0 - 24) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo-controlled Phase: Placebo |

Arm description:

Participants were randomized to receive placebo BID from day 1. Participants could also have received stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) and 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD).

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

Dosage and administration details:

Twice daily for 24 weeks

| | |
|------------------|--|
| Arm title | Placebo-controlled Phase: Apremilast 30 mg |
|------------------|--|

Arm description:

Participants were randomized to receive apremilast 30 mg BID from day 1. Participants could also have received stable doses of NSAIDs and 1 csDMARD.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla |
| Pharmaceutical forms | Buccal tablet |
| Routes of administration | Oral use |

Dosage and administration details:

30 mg twice daily \pm NSAID and/or \leq 1 csDMARD

| Number of subjects in period 1 | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg |
|---------------------------------|-----------------------------------|--|
| | | |
| Started | 105 | 203 |
| Full analysis set | 105 | 203 |
| Escaped early at week 16 | 24 ^[1] | 21 ^[2] |
| Completed week 16 and continued | 92 | 172 |
| Safety analysis set | 104 | 203 |
| Completed | 87 | 162 |
| Not completed | 18 | 41 |
| Consent withdrawn by subject | 4 | 7 |
| Adverse Event | 8 | 19 |
| Death | - | 1 |
| Pregnancy | - | 1 |
| Miscellaneous | - | 2 |
| Non-compliance with study drug | 1 | 1 |
| Lost to follow-up | - | 3 |
| Lack of efficacy | 4 | 7 |
| Protocol deviation | 1 | - |

Notes:

[1] - 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: This is the number of participants that at week 16 did not have SJC improvement and escaped early to receive apremilast 30 mg BID.

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

Period 2

| | |
|------------------------------|--------------------------------------|
| Period 2 title | Apremilast-Extension (Weeks 24 - 48) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | No |
| Arm title | Apremilast-extension Phase: Placebo then Apremilast 30 mg |

Arm description:

Participants were randomized to receive placebo in the placebo-controlled phase, and entered the open-label apremilast-extension phase to receive apremilast 30 mg BID from week 24 to week 48.

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

| | |
|--|--|
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla |
| Pharmaceutical forms | Buccal tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 30 mg twice daily \pm NSAIDs and/or ≤ 1 csDMARD | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Twice daily for 24 weeks | |
| Arm title | Apremilast-extension Phase: Continued Apremilast 30 mg |

Arm description:

Participants were randomized to receive apremilast 30 mg BID in the placebo-controlled phase, and entered the open-label apremilast-extension phase to continue on apremilast 30 mg BID from week 24 to week 48.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Apremilast |
| Investigational medicinal product code | |
| Other name | Otezla |
| Pharmaceutical forms | Buccal tablet |
| Routes of administration | Oral use |

Dosage and administration details:

30 mg twice daily \pm NSAIDs and/or ≤ 1 csDMARD

| Number of subjects in period 2 | Apremilast-extension Phase: Placebo then Apremilast 30 mg | Apremilast-extension Phase: Continued Apremilast 30 mg |
|---------------------------------------|---|--|
| Started | 87 | 162 |
| Received 1 dose of apremilast | 86 | 160 |
| Completed | 77 | 133 |
| Not completed | 10 | 29 |
| Consent withdrawn by subject | 1 | 7 |
| Adverse Event | 2 | 6 |
| Not specified | - | 7 |
| Lost to follow-up | 4 | 1 |
| Lack of efficacy | 3 | 8 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo-controlled Phase: Placebo |
|-----------------------|-----------------------------------|

Reporting group description:

Participants were randomized to receive placebo BID from day 1. Participants could also have received stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) and 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD).

| | |
|-----------------------|--|
| Reporting group title | Placebo-controlled Phase: Apremilast 30 mg |
|-----------------------|--|

Reporting group description:

Participants were randomized to receive apremilast 30 mg BID from day 1. Participants could also have received stable doses of NSAIDs and 1 csDMARD.

| Reporting group values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | Total |
|--|-----------------------------------|--|-------|
| Number of subjects | 105 | 203 | 308 |
| Age Categorical 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) | 87 | 172 | 259 |
| From 65-84 years | 18 | 31 | 49 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 50.2 | 51.3 | - |
| standard deviation | ± 13.03 | ± 12.25 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 51 | 118 | 169 |
| Male | 54 | 85 | 139 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 3 | 3 |
| Asian | 1 | 4 | 5 |
| Black or African American | 2 | 1 | 3 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| White | 99 | 192 | 291 |
| Not Collected or Unknown | 2 | 3 | 5 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 13 | 16 | 29 |
| Not Hispanic or Latino | 91 | 185 | 276 |
| Not Reported | 1 | 2 | 3 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo-controlled Phase: Placebo |
| Reporting group description: Participants were randomized to receive placebo BID from day 1. Participants could also have received stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) and 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD). | |
| Reporting group title | Placebo-controlled Phase: Apremilast 30 mg |
| Reporting group description: Participants were randomized to receive apremilast 30 mg BID from day 1. Participants could also have received stable doses of NSAIDs and 1 csDMARD. | |
| Reporting group title | Apremilast-extension Phase: Placebo then Apremilast 30 mg |
| Reporting group description: Participants were randomized to receive placebo in the placebo-controlled phase, and entered the open-label apremilast-extension phase to receive apremilast 30 mg BID from week 24 to week 48. | |
| Reporting group title | Apremilast-extension Phase: Continued Apremilast 30 mg |
| Reporting group description: Participants were randomized to receive apremilast 30 mg BID in the placebo-controlled phase, and entered the open-label apremilast-extension phase to continue on apremilast 30 mg BID from week 24 to week 48. | |

Primary: Percentage of Participants who Achieved a Clinical State of Minimal Disease Activity (MDA-Joints) Response at Week 16

| | |
|--|---|
| End point title | Percentage of Participants who Achieved a Clinical State of Minimal Disease Activity (MDA-Joints) Response at Week 16 |
| End point description: MDA is defined as tender joint counts (TJC) ≤ 1 and SJC ≤ 1 plus 3 of the following 5 criteria: 1. psoriasis body surface area (BSA) $\leq 3\%$ 2. patient's pain visual analogue scale (VAS) on a 100 mm scale ≤ 15 ; where 0 indicates 'no pain' and 100 indicates 'pain as severe as can be imagined' 3. patient's global assessment of disease activity on a 100 mm scale ≤ 20 , where 0 represents the lowest level of disease activity and 100 represents the highest. 4. physical function assessed by Health Assessment Questionnaire Disability Index (HAQ-DI) ≤ 0.5 ; where 0 represents normal or no difficulty and 3 represents an inability to perform 5. enthesitis count ≤ 1 based on the Leeds Enthesitis Index; where 0 means nontender and 6 indicates 6 tender tendon insertions. The full analysis set included all participants who were randomized as specified in the protocol. | |
| End point type | Primary |
| End point timeframe: Week 16 | |

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 16.0 | 33.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Apremilast versus Placebo |
| Statistical analysis description: Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per Interactive Web Response System (IWRS) data, using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on a normal approximation to the weighted average. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 18.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.9 |
| upper limit | 28.1 |

Notes:

[1] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Secondary: Percentage of Participants who Achieved Remission or Low Disease Activity at Week 16 Based on Clinical Activity in Psoriatic Arthritis (cDAPSA)

| | |
|---|---|
| End point title | Percentage of Participants who Achieved Remission or Low Disease Activity at Week 16 Based on Clinical Activity in Psoriatic Arthritis (cDAPSA) |
| End point description: The cDAPSA score is based on the numerical summation of 4 disease activity variables: tender and swollen joints, patient's global assessments of Disease Activity and Assessment of Pain (VAS). The cDAPSA score ranges from 0 to 154, with a higher score indicating more disease activity. cDAPSA remission is defined as a DAPSA score ≤ 4 and low disease activity is defined as a cDAPSA score > 4 but ≤ 13). The full analysis set included all participants who were randomized as specified in the protocol. | |
| End point type | Secondary |
| End point timeframe: Week 16 | |

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 51.8 | 70.2 | | |

Statistical analyses

| Statistical analysis title | Apremilast versus Placebo |
|----------------------------|---------------------------|
|----------------------------|---------------------------|

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

| | |
|---|--|
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0017 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 18.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7 |
| upper limit | 30.2 |

Notes:

[2] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Secondary: Percentage of Participants with SJC ≤ 1 at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Participants with SJC ≤ 1 at Week 16 |
|-----------------|--|

End point description:

The SJC was based on 66 joints and at week 16 is based on the sentinel joints (i.e., the joints that were affected at baseline). A SJC response is defined as a count ≤ 1.

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

End point timeframe:

Week 16

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 69.0 | 74.0 | | |

Statistical analyses

| Statistical analysis title | Apremilast versus Placebo |
|----------------------------|---------------------------|
|----------------------------|---------------------------|

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

| | |
|---|--|
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3539 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 5.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 16 |

Notes:

[3] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation

Secondary: Percentage of Participants with TJC ≤ 1 at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Participants with TJC ≤ 1 at Week 16 |
|-----------------|--|

End point description:

The TJC was based on 68 joints and at week 16 was based on the sentinel joints (i.e., the joints that were affected at baseline). A TJC response is defined as a count ≤ 1.

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

End point timeframe:

Week 16

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 44.4 | 66.2 | | |

Statistical analyses

| Statistical analysis title | Apremilast versus Placebo |
|--|--|
| Statistical analysis description: | |
| Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 22.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.4 |
| upper limit | 33.7 |

Notes:

[4] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Secondary: Percentage of Participants with an Assessment of Pain Score \leq 15 mm in VAS at Week 16

| | |
|--|--|
| End point title | Percentage of Participants with an Assessment of Pain Score \leq 15 mm in VAS at Week 16 |
| End point description: | |
| The Patients Pain VAS is the participant's assessment of how much pain they had, on average, during the last week in their joints due to psoriatic arthritis. The VAS score ranges from 0 to 100 mm, with a higher score indicating more pain. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 16 | |

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 13.1 | 29.4 | | |

Statistical analyses

| Statistical analysis title | Apremilast versus Placebo |
|--|--|
| Statistical analysis description: | |
| Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0022 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 16.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.9 |
| upper limit | 25.8 |

Notes:

[5] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Secondary: Percentage of Participants with Patient's Global Assessments of Disease Activity Score of ≤ 20 mm in the VAS at Week 16

| | |
|--|--|
| End point title | Percentage of Participants with Patient's Global Assessments of Disease Activity Score of ≤ 20 mm in the VAS at Week 16 |
| End point description: | |
| The Patient's Global Assessments of Disease Activity is an assessment of how active a participant's psoriatic arthritis was on average during the last week. It was assessed on a VAS ranging from 0 to 100 mm, with a higher score indicating more disease activity. A response is defined as a score ≤ 20 mm. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 16 | |

| | | | | |
|-----------------------------------|-----------------------------------|--|--|--|
| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 19.1 | 30.4 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Apremilast versus Placebo |
| Statistical analysis description: | |
| Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0286 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.7 |
| upper limit | 22 |

Notes:

[6] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Secondary: Change from Baseline in Psoriatic Arthritis Impact of Disease 12-item for Clinical Trials (PsAID-12) Questionnaire Score at Week 16

| | |
|---|---|
| End point title | Change from Baseline in Psoriatic Arthritis Impact of Disease 12-item for Clinical Trials (PsAID-12) Questionnaire Score at Week 16 |
| End point description: | |
| The PsAID-12 Questionnaire is a 12-item, self-administered questionnaire that reflects the impact of psoriatic arthritis from the perspective of the participant. The overall score ranges from 0 (best status) to 10 (worst status), with a cut-off ≤ 4 representing patient-acceptable symptom state. Analysis was based on a mixed-effects model for repeated measures (MMRM), which included treatment group, time, treatment group by time interaction, prior/concomitant use of csDMARD (naive, prior use only, both prior and concomitant use) and baseline glucocorticosteroid use (yes/no) per IWRS data as factors, and baseline value as a covariate. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 16 | |

| | | | | |
|-------------------------------------|-----------------------------------|--|--|--|
| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.42 (± 0.216) | -1.45 (± 0.178) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Apremilast versus Placebo |
| Statistical analysis description: | |
| Difference in least square (LS) means is based MMRM of the change from baseline. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | MMRM |
| Parameter estimate | Difference in LS means |
| Point estimate | -1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.48 |
| upper limit | -0.59 |

Secondary: Percentage of Participants with a Good or Moderate Psoriatic Arthritis Disease Activity (PASDAS) Score at Week 16

| | |
|---|---|
| End point title | Percentage of Participants with a Good or Moderate Psoriatic Arthritis Disease Activity (PASDAS) Score at Week 16 |
| End point description: | |
| The PASDAS is a weighted index comprising assessments of joints, function, acute-phase response, quality of life, and patient and physician VAS. The score range of the PASDAS is 0 - 10, with worse disease activity represented by higher scores. A good response is defined as a PASDAS score of ≤ 3.2 with improvement from baseline ≥ 1.6 points. A moderate response is defined as a PASDAS score > 3.2 with improvement from baseline ≥ 1.6 points; or PASDAS score < 5.4 with improvement from baseline ≥ 0.8 but < 1.6 points. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 16 | |

| End point values | Placebo-controlled Phase: Placebo | Placebo-controlled Phase: Apremilast 30 mg | | |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 42.7 | 59.9 | | |

Statistical analyses

| Statistical analysis title | Apremilast versus Placebo |
|--|--|
| Statistical analysis description: | |
| Adjusted difference in proportions is the weighted average of the treatment differences across strata formed by two stratification factors, prior/concomitant use of csDMARD and baseline glucocorticosteroid use per IWRS data, using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. | |
| Comparison groups | Placebo-controlled Phase: Placebo v Placebo-controlled Phase: Apremilast 30 mg |
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0043 ^[7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in proportions |
| Point estimate | 17.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.7 |
| upper limit | 29.7 |

Notes:

[7] - Two-sided p-value adjusted for prior/concomitant use of csDMARD and baseline glucocorticosteroid use, normalized via Wilson-Hilferty transformation.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 up to week 48 (end of extension phase), and a 4-week observational follow-up (up to 52 weeks).

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of study medication. For the placebo-controlled phase, participants were included in the treatment group for the treatment they actually received.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Placebo-Controlled: Placebo |
|-----------------------|-----------------------------|

Reporting group description: -

| | |
|-----------------------|---|
| Reporting group title | Apremilast-Exposure: Apremilast 30 mg BID |
|-----------------------|---|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Placebo-Controlled: Apremilast 30 mg BID |
|-----------------------|--|

Reporting group description: -

| Serious adverse events | Placebo-Controlled: Placebo | Apremilast- Exposure: Apremilast 30 mg BID | Placebo-Controlled: Apremilast 30 mg BID |
|---|--------------------------------|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 104 (5.77%) | 15 / 291 (5.15%) | 9 / 204 (4.41%) |
| number of deaths (all causes) | 0 | 2 | 2 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |
| General disorders and administration site conditions | | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |
| Injury, poisoning and procedural complications | | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 104 (0.96%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 2 / 291 (0.69%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 2 / 291 (0.69%) | 2 / 204 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | 0 / 291 (0.00%) | 0 / 204 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 1 / 204 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 291 (0.34%) | 0 / 204 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo-Controlled: Placebo | Apremilast- Exposure: Apremilast 30 mg BID | Placebo-Controlled: Apremilast 30 mg BID |
|---|--------------------------------|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 104 (17.31%) | 103 / 291 (35.40%) | 72 / 204 (35.29%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 104 (2.88%) | 21 / 291 (7.22%) | 16 / 204 (7.84%) |
| occurrences (all) | 3 | 40 | 28 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 104 (10.58%) | 69 / 291 (23.71%) | 47 / 204 (23.04%) |
| occurrences (all) | 13 | 82 | 51 |
| Nausea | | | |
| subjects affected / exposed | 4 / 104 (3.85%) | 28 / 291 (9.62%) | 22 / 204 (10.78%) |
| occurrences (all) | 5 | 32 | 26 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 104 (2.88%) | 19 / 291 (6.53%) | 7 / 204 (3.43%) |
| occurrences (all) | 4 | 19 | 7 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 February 2019 | <ul style="list-style-type: none">- Edited exclusion criteria for clarity and to add severe renal disease as a significant laboratory abnormality.- Added creatinine clearance to clinical laboratory evaluations to support edits to the exclusion criteria.- Modified vital signs, height and weight to clarify treatment discontinuation for severe weight loss. Measurement of weight was added for every visit and the table events and safety follow-up period were also revised.- Modified psychiatric evaluation to clarify study discontinuation for psychiatric symptoms.- Added Section 6.5.5 to clarify treatment discontinuation for severe symptoms of diarrhea, nausea and vomiting.- Added Section 8.2 to align with guidance provided in the label regarding co-administration of strong cytochrome P450 3A4 enzyme inducers with apremilast.- Updated inclusion criteria to clarify that contraception, Option 2, may not be acceptable as a highly effective contraception option in all countries per local guidelines/regulations.- Modified Section 6.5.1 Serum and Urine Pregnancy Tests for Females of Childbearing Potential to clarify that additional visits (unscheduled visits) may be done to monitor pregnancy testing. |
| 04 May 2020 | <ul style="list-style-type: none">- Removed all references that include "approved product labeling" and "Prescribing Information" to address feedback from Health Authorities.- Updated exclusion criteria to reflect that prior exposure to tyk2 inhibitors is prohibited. |
| 17 May 2020 | <ul style="list-style-type: none">- Removed all references to "Celgene Corporation" and replaced with "Amgen Inc".- Updated Cover Pages with Amgen contact information.- Updated Monitoring and Reporting of Adverse Events to align with Amgen Global Drug Safety processes.- Modified Section 10.4 Pregnancy according to Amgen Global Drug Safety processes.- Updated reporting of serious adverse events to include instructions for paper reporting.- Updated with Amgen emergency contact information.- Added Section 15.3 Product Complaint. |
| 03 February 2021 | <ul style="list-style-type: none">- Modified the timepoint for the primary endpoint from week 24 to week 16, which is closer to the timeframe in which clinicians assess efficacy in clinical practice.- Modified inclusion criteria to remove requirement that treatment with a maximum of 1 csDMARD (methotrexate or sulfasalazine) begin ≤ 6 months prior to baseline to allow for concomitant use of 1 csDMARD if the subject is on a stable regimen for at least 3 months prior to the baseline visit.- Modified exclusion criteria to allow prior use of > 1 csDMARD to treat conditions other than the study indication, such as psoriasis.- Modified the early diagnosis period from ≥ 3 months and ≤ 24 months to ≥ 3 months and ≤ 5 years.- Modified timepoints for secondary efficacy endpoints from week 24 to week 16. |

| | |
|--------------|--|
| 12 July 2021 | <ul style="list-style-type: none"> - Updated the total number of subjects to be randomized in the study from 330 subjects (220 on active treatment and 110 on placebo) to 285 subjects (190 on active treatment and 95 on placebo). - Updated the inclusion criterion regarding duration of disease to change "diagnosis" to "signs and symptoms" of PsA and to remove the minimum duration. - Updated the study rationale to include subjects with early diagnosis of PsA (≤ 5 years since signs and symptoms began). - Updated the exclusion criteria to allow prior use of 2 csDMARDs (as opposed to 1). - Updated the exclusion criteria to reflect exclusion of subjects with bacterial infections requiring treatment within 1 week of screening (previously within 4 weeks of screening). - Updated the table of events table to include a window of ± 7 days for the observational follow-up visit. |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported