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 ± NSAID and/or ≤ 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 ± 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 ± 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) ≤ 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 ≤ 15 mm in VAS at Week 16

End point title	Percentage of Participants with an Assessment of Pain Score ≤ 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: 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.

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

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	- 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	- 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	- 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	- 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	- 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