Clinical trial results:
A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) Monotherapy in Subjects with Active Psoriatic Arthritis

Summary

EudraCT number	2013-001590-25
Trial protocol	HU CZ ES EE
Global end of trial date	17 November 2016

Results information

Result version number	v1 (current)
This version publication date	03 December 2017
First version publication date	03 December 2017

Trial information

Trial identification

Sponsor protocol code	CC-10004-PSA-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01925768
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07907
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Nikolay Delev, MD, Celgene Corporation, 01 9088975662, NDelev@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	24 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of apremilast 30 mg BID monotherapy, compared with placebo, over 24 weeks of treatment, with the primary analysis at Week (Wk) 16, in subjects with active psoriatic arthritis

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents. Patient Confidentiality and Personal Data Protection, Informed Consent and Biomarker Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United States: 66
Worldwide total number of subjects	219
EEA total number of subjects	85

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)	191
From 65 to 84 years	27
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study consisted of a 24-week randomized, double-blind, placebo-controlled treatment phase, followed by a 28-week active treatment phase and a 52-week open-label extension phase, for an overall study duration of 113 weeks. 219 subjects were enrolled from 59 centers across 10 countries.

Pre-assignment

Screening details:

Randomized participants were stratified by their baseline prednisone use (yes or no) and by their previous disease modifying antirheumatic drug (DMARD) use (excluding biologics). Participants were allowed to take non-steroidal anti-inflammatory agents and/or low dose corticosteroids during the study.

Period 1

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

Blinding implementation details:

Subjects remained blinded to apremilast until week 52 or at discontinuation visit

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Apremilast (PBO)

Arm description:

Participants were randomized to placebo tablets twice daily (BID) during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape (EE), at the discretion of the investigator and transitioned onto apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape.

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:

Identically matching placebo tablets BID.

Arm title	Apremilast (APR)

Arm description:

Participants were randomized to apremilast 30 mg tablets BID during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and continued receiving apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind 24-week treatment phase entered into the blinded active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. All participants who completed the 52-week treatment phase entered into the open-label extension phase (Week 52 to Week 104) for an additional year continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

Arm type	Experimental

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

Dosage and administration details:

Apremilast 30 mg tablets BID.

Number of subjects in period 1	Placebo/Apremilast (PBO)	Apremilast (APR)
Started	109	110
Received Treatment	109	109
Completed Week 16	101	91
Escaped Early (EE)	35 [1]	13 [2]
Completed	98	87
Not completed	11	23
Consent withdrawn by subject	1	4
Adverse event, non-fatal	5	10
Non-compliance with study drug	-	1
Lost to follow-up	1	-
Protocol deviation	1	2
Lack of efficacy	3	6

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: Subjects were assessed for swollen and tender joints; those that met the early escape criteria were allowed to be transitioned to apremilast. Subjects who did not early escape, remained on placebo.
[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: Subjects were assessed for swollen and tender joints; those that met the early escape criteria were allowed to be transitioned to apremilast. Subjects who did not early escape, remained on placebo.

Period 2

Period 2 title	ActiveTreatment/Extension (Weeks 24-104)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Subjects remained blinded to apremilast until week 52 or at discontinuation visit

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo/Apremilast

Arm description:

Participants were randomized to placebo tablets twice daily during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and transitioned onto apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind, 24-week treatment phase entered into the blinded, active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. Participants who completed the active treatment phase entered into the open-label extension phase for an additional year (Week 52 to Week 104) continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

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:

Identically matching placebo tablets BID.

Arm title	Apremilast

Arm description:

Participants were randomized to apremilast 30 mg tablets BID during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and continued receiving apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind 24-week treatment phase entered into the blinded active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. All participants who completed the 52-week treatment phase entered into the open-label extension phase (Week 52 to Week 104) for an additional year continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID.

Number of subjects in period 2[3]	Placebo/Apremilast	Apremilast
Started	95	85
Completed	75	67
Not completed	20	18
Adverse event, serious fatal	-	1
Consent withdrawn by subject	7	9
Adverse event, non-fatal	5	1
Lost to follow-up	2	1
Lack of efficacy	6	6

Notes:

[3] - 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: Five subjects from the placebo-controlled period elected not to participate in the active treatment phase.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Apremilast (PBO)

Reporting group description:

Participants were randomized to placebo tablets twice daily (BID) during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape (EE), at the discretion of the investigator and transitioned onto apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape.

Reporting group title	Apremilast (APR)

Reporting group description:

Participants were randomized to apremilast 30 mg tablets BID during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and continued receiving apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind 24-week treatment phase entered into the blinded active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. All participants who completed the 52-week treatment phase entered into the open-label extension phase (Week 52 to Week 104) for an additional year continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

Reporting group values	Placebo/Apremilast (PBO)	Apremilast (APR)	Total
Number of subjects	109	110	219
Age categorical Units: Subjects			
Adults (18-64 years)	97	94	191
From 65-84 years	11	16	27
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	48.0	50.7	
standard deviation	± 13.75	± 12.22	-
Gender, Male/Female Units: Subjects			
Female	65	58	123
Male	44	52	96
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	1	0	1
White	105	109	214
More than one race	0	0	0
Unknown or Not Reported	2	0	2
Study Specific Characteristic | Duration of Psoriatic Arthritis			
Duration of Psoriatic Arthritis is reported as the time since diagnosis			
Units: years			
arithmetic mean	3.59	4.04	

standard deviation	± 5.497	± 4.482	-

End points reporting groups

Reporting group title	Placebo/Apremilast (PBO)

Reporting group description:

Participants were randomized to placebo tablets twice daily (BID) during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape (EE), at the discretion of the investigator and transitioned onto apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape.

Reporting group title	Apremilast (APR)

Reporting group description:

Participants were randomized to apremilast 30 mg tablets BID during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and continued receiving apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind 24-week treatment phase entered into the blinded active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. All participants who completed the 52-week treatment phase entered into the open-label extension phase (Week 52 to Week 104) for an additional year continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

Reporting group title	Placebo/Apremilast

Reporting group description:

Participants were randomized to placebo tablets twice daily during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and transitioned onto apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind, 24-week treatment phase entered into the blinded, active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. Participants who completed the active treatment phase entered into the open-label extension phase for an additional year (Week 52 to Week 104) continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

Reporting group title	Apremilast

Reporting group description:

Participants were randomized to apremilast 30 mg tablets BID during the double-blind, 24-week placebo-controlled phase. Those whose improvement was less than 10% in both swollen and tender joint counts at Week 16 were eligible for early escape, at the discretion of the investigator and continued receiving apremilast 30 mg BID in a blinded fashion. Those who had a 10% or more improvement in either swollen or tender joint counts at Week 16 were not eligible for early escape. Participants who completed the double-blind 24-week treatment phase entered into the blinded active treatment phase for an additional 28 weeks (Week 24 to Week 52) and continued receiving Apremilast 30 mg tablets BID. All participants who completed the 52-week treatment phase entered into the open-label extension phase (Week 52 to Week 104) for an additional year continuing to receive apremilast 30 mg tablets BID until the end of the study (up to Week 104 visit) or until early discontinuation.

Subject analysis set title	Number of subjects with TEAEs in the apremilast-exposure phase
Subject analysis set type	Safety analysis

Subject analysis set description:

A TEAE is an AE with a start date on or after the date of the first dose of Investigational Product (IP). An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. 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. Safety population.

Primary: Percentage of Participants Who Achieved an American College of Rheumatology 20% (ACR20) Response at Week 16

End point title	Percentage of Participants Who Achieved an American College of Rheumatology 20% (ACR20) Response at Week 16

End point description:

Percentage of participants with an American College of Rheumatology 20% (ACR20) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 20% improvement in 78 tender joint count; • ≥ 20% improvement in 76 swollen joint count; and • ≥ 20% improvement in at least 3 of the 5 following parameters: o Patient's self-assessment of pain (measured on a 0 to 10 unit numeric rating scale [NRS]); o Patient's global self-assessment of disease activity (measured on a 0 to 10 unit NRS); o Physician's global assessment of disease activity (measured on a 0 to 10 unit NRS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]); o C-Reactive Protein (CRP) Those who withdrew early or who did not have sufficient data at Week 16 were counted as non-responders. Full Analysis Set (FAS) population consisting of all participants randomized as specified in the protocol.

End point type	Primary

End point timeframe:

Baseline and Week 16

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: percentage of participants				
number (not applicable)	20.2	38.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.004 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	29.3

Notes:

[1] - Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by the 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights. The CI is based on a normal approximation.
[2] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24

End point description:

HAQ-DI is a patient-reported questionnaire consisting of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task are summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. A higher score indicates worse physical functioning, and a negative change from baseline indicates improvement. Full analysis set; Participants with a baseline and at least 1 postbaseline value during the placebo-controlled phase were included in the analysis (mixed effects model for repeated measure [MMRM])

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: units on a scale				
least squares mean (standard error)	0.169 (± 0.0581)	-0.273 (± 0.0572)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean (SE) and 2-sided p-value were based on a MMRM analysis for change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD and baseline corticosteroids used as factors and baseline value as a covariate

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1677
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.251
upper limit	0.044

Notes:

[3] - Those with a baseline and at least 1 postbaseline value at the PBO controlled phase were counted with mixed effects model for repeated measure (MMRM)

Secondary: Percentage of participants who Achieved an American College of Rheumatology 20% (ACR20) at Week 24

End point title	Percentage of participants who Achieved an American College

	of Rheumatology 20% (ACR20) at Week 24

End point description:

Percentage of participants with an American College of Rheumatology 20% (ACR20) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 20% improvement in 78 tender joint count; • ≥ 20% improvement in 76 swollen joint count; and • ≥ 20% improvement in at least 3 of the 5 following parameters: o Patient's self-assessment of pain (measured on a 0 to 10 unit numeric rating scale [NRS]); o Patient's global self-assessment of disease activity (measured on a 0 to 10 unit NRS); o Physician's global assessment of disease activity (measured on a 0 to 10 unit NRS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]); o C-Reactive Protein (CRP) Those who withdrew early or who did not have sufficient data at Week 16 were counted as non-responders. FAS population.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: percentage of participants				
number (not applicable)	24.8	43.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by the 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights. The CI is based on a normal approximation.

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.004 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	30.6

Notes:

[4] - Those who withdrew early or who did not have sufficient data at Week 16 were counted as non-responders.
[5] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Secondary: Change From Baseline in the 28-joint Disease Activity Score using C-reactive protein as the acute-phase reactant (DAS28 [CRP]) at Week 24

End point title	Change From Baseline in the 28-joint Disease Activity Score

	using C-reactive protein as the acute-phase reactant (DAS28 [CRP]) at Week 24

End point description:

The DAS28 measures the severity of disease at a specific time and is derived from the following variables: • 28 tender joint count • 28 swollen joint count, which do not include the DIP joints, the hip joint, or the joints below the knee; • C-reactive protein (CRP) • Patient's global assessment of disease activity. DAS28 (CRP) scores range from 0 to 9.4. A DAS28 score higher than 5.1 indicates high disease activity, a DAS28 score less than 3.2 indicates low disease activity, and a DAS28 score less than 2.6 indicates clinical remission. A higher value indicates higher disease activity, and a negative change from baseline indicates improvement. Full analysis set; Participants with a baseline value and at least one post-baseline value (after exclusion of data for early escaped participants) during the placebo-controlled phase are included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	109		
Units: units on a scale				
least squares mean (standard error)	-0.76 (± 0.140)	-1.26 (± 0.138)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean (SE) and 2-sided p-value were based on a MMRM analysis for change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD and baseline corticosteroids used as factors and baseline value as a covariate.

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.15

Secondary: Change From Baseline in the Medical Outcomes Short Form Health Survey (SF-36) V2 Physical Function Domain Score at Week 24

End point title	Change From Baseline in the Medical Outcomes Short Form

	Health Survey (SF-36) V2 Physical Function Domain Score at Week 24

End point description:

The SF-36 (v 2.0) is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). Norm-based scores were used in analyses, calibrated so that 50 is the average score and the standard deviation equals 10. Higher scores indicate a higher level of functioning. The physical functioning domain assesses limitations in physical activities because of health problems. A positive change from baseline score indicates an improvement. Full analysis set; Participants with a baseline and at least 1 postbaseline value during the placebo-controlled phase were included in the analysis (mixed effects model for repeated measure [MMRM]).

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: units on a scale				
least squares mean (standard error)	1.26 (± 0.908)	3.94 (± 0.888)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean (SE) and 2-sided p-value were based on a MMRM analysis for change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD and baseline corticosteroids used as factors and baseline value as a covariate

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0167 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	4.88

Notes:

[6] - Those with a baseline and at least 1 postbaseline value at the PBO controlled phase were counted with mixed effects model for repeated measure (MMRM)

Secondary: Change From Baseline in the 36-item SF-36 Physical Component Summary Score at Week 24

End point title	Change From Baseline in the 36-item SF-36 Physical Component Summary Score at Week 24

End point description:

The SF-36 (v 2.0) is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The physical component summary (PCS) score includes the physical functioning, role physical, bodily pain, and general health domains. Minimum clinically important difference (MCID) for the scale scores, as well as the PCS and MCS, is defined as a 2.5-point improvement (increase) from baseline. Full analysis set. Subjects with a baseline value and at least one post-baseline value (after exclusion of data for early escaped subjects) during the placebo-controlled phase are included in the MMRM model.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	106		
Units: units on a scale				
least squares mean (standard error)	1.60 (± 0.959)	5.00 (± 0.949)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

2-sided 95% CI for the difference in LS mean.

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	5.7

Notes:

[7] - Based on an MMRM model for the change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD use and baseline Oral Corticosteroids use as factors and the baseline value as a covariate.

Secondary: Change from Baseline in the Duration of Morning Stiffness at Week 24

End point title	Change from Baseline in the Duration of Morning Stiffness at Week 24

End point description:

Morning stiffness was the participant’s assessment of how long their morning stiffness lasted after first waking up in the morning, on average, during the previous week. A higher value indicates longer duration, and a negative change from baseline indicates improvement. Full Analysis Set; Analysis includes participants with a baseline and at least one post-baseline value; last observation carried

forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: minutes				
arithmetic mean (standard deviation)	21.9 (± 137.11)	-5.7 (± 83.41)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [8]
Method	Sign test
Parameter estimate	Mean difference (final values)
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.5
upper limit	10.2

Notes:

[8] - p-value based on distribution free signed rank test

Secondary: Percentage of Participants with Improved Change in Severity of Morning Stiffness at Week 24

End point title	Percentage of Participants with Improved Change in Severity of Morning Stiffness at Week 24

End point description:

Morning stiffness severity was the participant’s assessment of how severe their morning stiffness was after first waking up in the morning, on average, during the previous week. The severity was recorded as none, mild, moderate, moderately severe, or very severe. The response of no improvement includes subjects who had no change or worsened. Improvement is defined as the change from baseline of a more severe assessment to less severe assessment. Full Analysis Set; Participants who withdrew early or who did not have sufficient data at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: percentage of participants				
number (not applicable)	20.2	40.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by the 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights. The CI is based on a normal approximation.

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	31.3

Notes:

[9] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline oral corticosteroids (prednisone or equivalent) use.

Secondary: Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16

End point title	Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16

End point description:

HAQ-DI is a patient-reported questionnaire consisting of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task are summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. A higher score indicates worse physical functioning, and a negative change from baseline indicates improvement. Full analysis set; participants with a baseline value and at least 1 postbaseline value during the placebo-controlled phase were included in the mixed effects model for repeated measures (MRMM).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: units on a scale				
least squares mean (standard error)	0.055 (± 0.0513)	-0.205 (± 0.0523)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean (SE) and 2-sided p-value were based on a MMRM analysis for change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD and baseline corticosteroids used as factors and baseline value as a covariate

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0229
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.279
upper limit	-0.021

Secondary: Change From Baseline in the Disease Activity Score DAS28 (CRP) at Week 16

End point title	Change From Baseline in the Disease Activity Score DAS28 (CRP) at Week 16

End point description:

The DAS28 measures the severity of disease at a specific time and is derived from the following variables: • 28 tender joint count • 28 swollen joint count, which do not include the DIP joints, the hip joint, or the joints below the knee; • C-reactive protein (CRP) • Patient's global assessment of disease activity. DAS28 (CRP) scores range from 0 to 9.4. A DAS28 score higher than 5.1 indicates high disease activity, a DAS28 score less than 3.2 indicates low disease activity, and a DAS28 score less than 2.6 indicates clinical remission. A negative change from baseline indicates improvement. Full analysis set; participants with a baseline value and at least 1 postbaseline value during the placebo-controlled phase were included in the mixed effects model for repeated measures (MRMM).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	109		
Units: units on a scale				
least squares mean (standard error)	-0.39 (± 0.129)	-1.07 (± 0.133)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on an MMRM model for the change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use as factors and the baseline value as a covariate

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.35

Secondary: Change From Baseline in 36-item Short Form Health Survey (SF-36) V 2 Physical Functioning Domain at Week 16

End point title	Change From Baseline in 36-item Short Form Health Survey (SF-36) V 2 Physical Functioning Domain at Week 16

End point description:

The SF-36 (v 2.0) is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). Norm-based scores were used in analyses, calibrated so that 50 is the average score and the standard deviation equals 10. Higher scores indicate a higher level of functioning. The physical functioning domain assesses limitations in physical activities because of health problems. A positive change from Baseline score indicates an improvement. Full analysis set; participants with a baseline value and at least 1 postbaseline value during the placebo-controlled phase were included in the mixed effects model for repeated measures (MRMM).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: units on a scale				
least squares mean (standard error)	-1.04 (± 0.927)	2.43 (± 0.962)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by the 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights	
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	5.8

Secondary: Mean Change From Baseline in the Duration of Morning Stiffness at Week 16

End point title	Mean Change From Baseline in the Duration of Morning Stiffness at Week 16
End point description:	
Morning stiffness was the participant’s assessment of how long their morning stiffness lasted after first waking up in the morning, on average, during the previous week. A higher value indicates longer duration, and a negative change from baseline indicates improvement. Full analysis set; Analysis includes participants with a baseline and at least one post-baseline value; last observation carried forward (LOCF) imputation was used.	
End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: minutes				
arithmetic mean (standard deviation)	21.7 (± 136.85)	-7.2 (± 60.73)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0168 [11]
Method	Stratified Van Elteren test
Parameter estimate	Mean difference (final values)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[10] - Location shift and 95% CI based on Hodges-Lehmann for between treatment median estimates.

[11] - p-value based on stratified Van Elteren test, using 2 stratification factors: previous DMARD use and baseline Oral Corticosteroids

Secondary: Percentage of Participants Whose Severity of Morning Stiffness at Week 16 Improved from Baseline

End point title	Percentage of Participants Whose Severity of Morning Stiffness at Week 16 Improved from Baseline

End point description:

Morning stiffness severity was the participant's assessment of how severe their morning stiffness was after first waking up in the morning, on average, during the previous week. The severity was recorded as none, mild, moderate, moderately severe, or very severe. Improvement is defined as the change from baseline of a more severe assessment to less severe assessment. Full Analysis Set; Participants who discontinued early prior to Week 16 and those who did not have sufficient data for a definitive determination of response status at Week 16 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: percentage of participants				
number (not applicable)	25.7	46.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by the 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights.

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	32.8

Notes:

[12] - 2 sided-p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Secondary: Percentage of participants who Achieved an American College of Rheumatology 20% (ACR20) Response at Weeks 2, 4, 6, 8, 12 and 20

End point title	Percentage of participants who Achieved an American College of Rheumatology 20% (ACR20) Response at Weeks 2, 4, 6, 8, 12 and 20

End point description:

Percentage of participants with an American College of Rheumatology 20% (ACR20) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 20% improvement in 78 tender joint count; • ≥ 20% improvement in 76 swollen joint count; and • ≥ 20% improvement in at least 3 of the 5 following parameters: o Patient's self-assessment of pain (measured on a 0 to 10 unit numeric rating scale [NRS]); o Patient's global self-assessment of disease activity (measured on a 0 to 10 unit NRS); o Physician's global assessment of disease activity (measured on a 0 to 10 unit NRS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]); o C-Reactive Protein (CRP). Full analysis set; participants discontinued early prior to the visit and participants who did not have sufficient data for a definitive determination of response status for the visit were counted as nonresponders.

End point type	Secondary

End point timeframe:

Baseline and at Weeks 2, 4, 6, 8, 12 and 20

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: percentage of participants				
number (not applicable)				
Week 2	6.4	16.4		
Week 4	15.6	24.5		
Week 6	19.3	37.3		
Week 8	22.9	36.4		
Week 12	28.4	40.0		
Week 20	24.8	43.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0252 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	17.7

Notes:

[13] - Week 2; 2-sided 95% CI is based on a normal approximation to the weighted average

[14] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.1121 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	8.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	18.9

Notes:

[15] - Week 4; 2-sided 95% CI is based on a normal approximation to the weighted average

[16] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0036 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	29.3

Notes:

[17] - Week 6; 2-sided 95% CI is based on a normal approximation to the weighted average

[18] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights

Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0392 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	24.6

Notes:

[19] - Week 8; 2-sided 95% CI is based on a normal approximation to the weighted average

[20] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 12; 2-sided 95% CI is based on a normal approximation to the weighted average	
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0884 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	23.2

Notes:

[21] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Adjusted difference in proportions is the weighted average of the treatment differences across 4 strata by 2 stratification factors: previous DMARD use and baseline Corticosteroids use using CMH weights	
Comparison groups	Placebo/Apremilast (PBO) v Apremilast (APR)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	30.7

Notes:

[22] - Two-sided p-value is based on the Cochran-Mantel-Haenszel test adjusting for previous DMARD use and baseline Oral Corticosteroids (Prednisone or equivalent) use.

Secondary: Percentage of Participants Who Achieved an American College of Rheumatology 20% (ACR20) Response at Weeks 52 and 104

End point title	Percentage of Participants Who Achieved an American College of Rheumatology 20% (ACR20) Response at Weeks 52 and 104

End point description:

Percentage of participants with an American College of Rheumatology 20% (ACR20) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 20% improvement in 78 tender joint count; • ≥ 20% improvement in 76 swollen joint count; and • ≥ 20% improvement in at least 3 of the 5 following parameters: o Patient's self-assessment of pain (measured on a 0 to 10 unit numeric rating scale [NRS]); o Patient's global self-assessment of disease activity (measured on a 0 to 10 unit NRS); o Physician's global assessment of disease activity (measured on a 0 to 10 unit NRS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]); o C-Reactive Protein (CRP). Apremilast Participants as Randomized or Transitioned, which includes all participants who randomized or escaped/transitioned (at Week 16 or

Week 24) to apremilast, and with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	79		
Units: percentage of partcipants				
number (confidence interval 95%)				
Week 52	60.0 (49.1 to 70.2)	67.1 (55.6 to 77.3)		
Week 104, N=74, 69	66.2 (54.3 to 76.8)	59.4 (46.9 to 71.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Weeks 52 and 104

End point title	Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Weeks 52 and 104

End point description:

HAQ-DI is a patient-reported questionnaire consisting of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task are summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. A higher score indicates worse physical functioning, and a negative change from baseline indicates improvement. Apremilast participants as randomized or transitioned; The Placebo/Apremilast 30 mg BID group includes participants initially randomized to placebo and switched to apremilast 30 mg BID at Week 16 or 24 and with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	80		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 52	-0.323 (± 0.5759)	-0.395 (± 0.5297)		

Week 104, N=75, 69	-0.382 (± 0.5639)	-0.357 (± 0.6102)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Disease Activity Score (DAS28) at Week 52 and 104

End point title	Change From Baseline in the Disease Activity Score (DAS28) at Week 52 and 104

End point description:

The DAS28 measures the severity of disease at a specific time and is derived from the following variables: • 28 tender joint count • 28 swollen joint count, which do not include the DIP joints, the hip joint, or the joints below the knee; • C-reactive protein (CRP) • Patient's global assessment of disease activity. DAS28 (CRP) scores range from 0 to 9.4. A DAS28 score higher than 5.1 indicates high disease activity, a DAS28 score less than 3.2 indicates low disease activity, and a DAS28 score less than 2.6 indicates clinical remission. A negative change from baseline indicates improvement. Apremilast participants as randomized or transitioned. The Placebo/Apremilast30 mg BID group includes participants initially randomized to placebo and switched to apremilast 30 mg BID at Week 16 or 24 and with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	79		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 52	-1.46 (± 0.985)	-1.71 (± 1.054)		
Week 104, N=73, 69	-1.62 (± 10.86)	-1.70 (± 1.035)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 36-item SF-36 (V2.0) Physical Functioning Domain Score at Weeks 52 and 104

End point title	Change From Baseline in 36-item SF-36 (V2.0) Physical Functioning Domain Score at Weeks 52 and 104

End point description:

The SF-36 (v 2.0) is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental

health, vitality, social function, physical and emotional health). Norm-based scores were used in analyses, calibrated so that 50 is the average score and the standard deviation equals 10. Higher scores indicate a higher level of functioning. The physical functioning domain assesses limitations in physical activities because of health problems. A positive change from Baseline score indicates an improvement. Apremilast Subjects as Randomized or Transitioned; The Placebo/30 mg BID group includes participants initially randomized to placebo and switched to apremilast 30 mg BID at Week 16 or 24and with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	80		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 52	5.11 (± 9.842)	6.00 (± 9.990)		
Week 104, N= 75, 69	5.78 (± 9.932)	5.95 (± 10.827)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Duration of Morning Stiffness at Weeks 52 and 104

End point title	Change From Baseline in the Duration of Morning Stiffness at Weeks 52 and 104

End point description:

Morning stiffness was the participant’s assessment of how long their morning stiffness lasted after first waking up in the morning, on average, during the previous week. A higher value indicates longer duration, and a negative change from baseline indicates improvement. Apremilast participants as randomized or transitioned; The Placebo/ Apremilast 30 mg BID group includes participants initially randomized to placebo and switched to apremilast 30 mg BID at Week 16 or 24 And with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	80		
Units: minutes				
arithmetic mean (standard deviation)				
Week 52	3.3 (± 174.11)	-5.7 (± 93.62)		

Week 104, N-75, 69	-11.9 (± 165.36)	-7.0 (± 71.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants whose severity of morning stiffness at Week 52 and 104 improved from baseline

End point title	Percentage of participants whose severity of morning stiffness at Week 52 and 104 improved from baseline

End point description:

Morning stiffness severity was the participant’s assessment of how severe their morning stiffness was after first waking up in the morning, on average, during the previous week. The severity was recorded as none, mild, moderate, moderately severe, or very severe. Improvement is defined as the change from baseline of a more severe assessment to less severe assessment. Apremilast participants as randomized or transitioned. The Placebo/30 mg BID group includes subjects initially randomized to placebo and switched to apremilast 30 mg BID at Week 16 or 24 and with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 52 and 104

End point values	Placebo/Apremilast	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	80		
Units: percentage of participants				
number (not applicable)				
Week 52	57.1	57.5		
Week 104, N= 75, 69	50.7	59.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment Emergent Adverse Events (TEAE) during the 24 week placebo controlled phase

End point title	Number of participants with Treatment Emergent Adverse Events (TEAE) during the 24 week placebo controlled phase

End point description:

A TEAE is an AE with a start date on or after the date of the first dose of IP. An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE (SAE) 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 or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Safety population = participants who were randomized and received at least one dose of IP.

End point type	Secondary

End point timeframe:

Date of first dose of study drug to Week 24; median duration of exposure during placebo controlled phase was 24.14 weeks

End point values	Placebo/Apremilast (PBO)	Apremilast (APR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: Participants				
Any TEAE	69	73		
Any drug-related TEAE	18	30		
Any severe TEAE	4	2		
Any serious TEAE	5	3		
Any serious drug-related TEAE	0	0		
Any TEAE leading to study drug withdrawal	5	10		
Any TEAE leading to study dose interruption	7	10		
Any TEAE leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment Emergent Adverse Events (TEAE) during the apremilast-exposure period

End point title	Number of participants with Treatment Emergent Adverse Events (TEAE) during the apremilast-exposure period

End point description:

A TEAE is an AE with a start date on or after the date of the first dose of Investigational Product (IP). An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an 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. Safety population

End point type	Secondary

End point timeframe:

Start of first dose of IP up to week 104: Weeks 0 to104 for those initially randomized to APR 30 mg BID, Weeks 16 -104 for PBO-treated patients who EE to APR at Week 16 and from Weeks 24-104 for PBO-treated patients who transitioned to APR at Week 24.

End point values	Number of subjects with TEAEs in the apremilast-exposure phase			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: particpants				
number (not applicable)				
Any TEAE	157			
Any drug-related TEAE	52			
Any severe TEAE	8			
Any serious TEAE	15			
Any serious drug-related TEAE	0			
Any TEAE leading to study dose interruption	28			
Any TEAE leading to study drug withdrawal	17			
Any TEAE leading to death	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's are reported:
1. Placebo-controlled phase (Weeks 0-24)
2. Up to 104 weeks for all participants randomized or transitioned onto apremilast at any time during the study (apremilast-exposure phase). AEs were monitored for 37 months

Adverse event reporting additional description:

Median duration of exposure during the placebo-controlled phase was 24.14 weeks and 81 weeks during the apremilast exposure phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	V14.0

Reporting groups

Reporting group title	Placebo-Controlled Phase: Placebo (Weeks 0-24)

Reporting group description:

Participants who were randomized to placebo tablets twice daily (BID) during the double-blind, 24-week placebo-controlled phase.

Reporting group title	Apremilast Exposure Period: Apremilast (Weeks 0-104)

Reporting group description:

Participants who received apremilast any point during the course of the study, on Day 0, 16 or Day 24 and continued to receive apremilast 30 mg tablets BID up to week 104.

Reporting group title	Placebo-Controlled Phase: Apremilast (Weeks 0-24)

Reporting group description:

Participants who were randomized to apremilast tablets twice daily during the double-blind, 24-week placebo-controlled phase.

Serious adverse events	Placebo-Controlled Phase: Placebo (Weeks 0-24)	Apremilast Exposure Period: Apremilast (Weeks 0-104)	Placebo-Controlled Phase: Apremilast (Weeks 0-24)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 109 (4.59%)	15 / 206 (7.28%)	3 / 109 (2.75%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Prostate cancer			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Respiratory papilloma			
subjects affected / exposed	1 / 109 (0.92%)	1 / 206 (0.49%)	0 / 109 (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
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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
Head injury			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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			
Arteriosclerosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Cardiomyopathy alcoholic			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Coronary artery disease			
subjects affected / exposed	0 / 109 (0.00%)	2 / 206 (0.97%)	0 / 109 (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
Hypertensive heart disease			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Myocardial infarction			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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			
Chest pain			
subjects affected / exposed	1 / 109 (0.92%)	0 / 206 (0.00%)	0 / 109 (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
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Osteoarthritis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
Infections and infestations			

Arthritis infective			
subjects affected / exposed	0 / 109 (0.00%)	1 / 206 (0.49%)	0 / 109 (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 Phase: Placebo (Weeks 0-24)	Apremilast Exposure Period: Apremilast (Weeks 0-104)	Placebo-Controlled Phase: Apremilast (Weeks 0-24)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 109 (33.94%)	83 / 206 (40.29%)	41 / 109 (37.61%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 109 (6.42%)	13 / 206 (6.31%)	7 / 109 (6.42%)
occurrences (all)	7	13	7
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 109 (3.67%)	13 / 206 (6.31%)	8 / 109 (7.34%)
occurrences (all)	5	16	11
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 109 (11.01%)	34 / 206 (16.50%)	16 / 109 (14.68%)
occurrences (all)	13	52	22
Nausea			
subjects affected / exposed	2 / 109 (1.83%)	18 / 206 (8.74%)	9 / 109 (8.26%)
occurrences (all)	2	21	10
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 109 (2.75%)	11 / 206 (5.34%)	5 / 109 (4.59%)
occurrences (all)	3	11	5
Nasopharyngitis			
subjects affected / exposed	7 / 109 (6.42%)	17 / 206 (8.25%)	9 / 109 (8.26%)
occurrences (all)	7	24	11
Upper respiratory tract infection			
subjects affected / exposed	11 / 109 (10.09%)	17 / 206 (8.25%)	5 / 109 (4.59%)
occurrences (all)	13	19	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2013	•Inclusion Criterion 7 was changed to reflect hsCRP ≥ 0.2 mg/dL at Screening •The analysis of the secondary endpoint of SF-36v2 physical component summary score was described in the SAP •Visit windows were removed from the footnotes and incorporated into the header of the Table of Events •Reflex test was added if hepatitis C antibody test was positive •Bristol Stool Scale and Stool Diary were removed from the protocol •TEAEs of Special Interest were added for TEAEs of diarrhea and similar events •ESR was added to calculate DAS28 for exploratory analysis •Clarification was made on the calculation of DAS28 •Exclusion Criterion 12 was revised to add "no new or recurrent infections prior to baseline visit" •Overdose reporting in drug exposure eCRF page was removed •Modification was made on Section 8.6, Investigational Product Accountability and Disposal •Correction on NSAIDs or narcotic analgesics use was made •Use of topical corticosteroids as background therapy was changed from "all" to "low potency" topical corticosteroids •TEAEs of diarrhea were added to the Monitoring, Recording and Reporting of TEAE section •Citations were updated •Administrative and spelling corrections were made

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported