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

Summary

EudraCT number	2010-018386-32
Trial protocol	CZ EE GB BE DE HU ES IT PL BG
Global end of trial date	26 January 2017

Results information

Result version number	v1 (current)
This version publication date	11 February 2018
First version publication date	11 February 2018

Trial information

Trial identification

Sponsor protocol code	CC-10004-PSA-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01212757
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	ClinicalTrialDisclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	Nikolay Delev, MD, Celgene Corporation, 01 908-897-5662, 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	10 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the clinical efficacy of 2 doses of apremilast (APR) (20 mg or 30 mg orally twice daily [BID]), compared with placebo (PBO), on the signs and symptoms of Psoriatic Arthritis (PsA) after administration for16 weeks.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Czech Republic: 88
Country: Number of subjects enrolled	Estonia: 66
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 75

Worldwide total number of subjects	488
EEA total number of subjects	314

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)	440
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was a multicenter study with 84 sites from the United States, Canada, Europe, Russia, Australia, South Africa and Taiwan.

Pre-assignment

Screening details:

This study consisted of a 24-week randomized, double-blind, placebo-controlled phase, a 28-week randomized, double-blind active treatment phase and a 4-year open-label safety phase, for an overall study duration of 5 years.

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, Subject

Blinding implementation details:

Blinding to treatment assignment was maintained at all sites until after the Week 52 database lock at Year 1, after all Week 52 analyses were completed and the results were released. At that time, active medication was provided. The blind was otherwise not to be broken during the study unless, in the opinion of the doctor, it was necessary to safely treat the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants initially randomized to placebo tablets twice daily (BID) in the 24-week placebo-controlled phase. Participants who did not have at least 20% improvement in swollen and tender joint counts at Week (Wk) 16 were re-randomized to either 20 mg or 30 mg apremilast twice daily [(early escape (EE)].

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

Dosage and administration details:

Placebo tablets (identical in appearance to apremilast) twice daily.

Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.

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 twice daily.

Number of subjects in period 1	Placebo	Apremilast 20 mg	Apremilast 30 mg
Started	162	163	163
Received Treatment	159	163	162
Completed Week 16	148	151	149
Early Escape at Week 16	88 [1]	59 [2]	64 [3]
Completed	143	143	142
Not completed	19	20	21
Consent withdrawn by subject	7	9	3
Adverse event, non-fatal	4	5	12
Miscellaneous	1	2	-
Lost to follow-up	1	1	2
Randomization Error	3	-	1
Lack of efficacy	3	2	2
Protocol deviation	-	1	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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

[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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

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

Justification: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

Period 2

Period 2 title	Active Treatment Phase (Weeks 24 - 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Blinding to treatment assignment was maintained at all sites until after the Week 52 database lock at Year 1, after all Week 52 analyses were completed and the results were released. At that time, active medication was provided. The blind was otherwise not to be broken during the study unless, in the opinion of the doctor, it was necessary to safely treat the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily in the active treatment/long-term safety phase.

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

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 twice daily.

Arm title	Placebo / Apremilast 20 mg EE

Arm description:

Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized due to early escape (EE) at Week 16 to receive 20 mg apremilast twice daily during the active treatment phase.

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 20 mg tablets twice a day.

Arm title	Placebo / Apremilast 20 mg XO

Arm description:

Participants initially randomized to receive placebo twice daily in the 24-week placebo-controlled phase were re-randomized at Week 24 (XO) to receive 20 mg apremilast twice daily during the active treatment phase.

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 20 mg tablets twice a day.

Arm title	Placebo / Apremilast 30 mg EE

Arm description:

Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized due to early escape (EE) at Week 16 to receive 30 mg apremilast twice daily during the active treatment phase.

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 twice a day

Arm title	Placebo / Apremilast 30 mg XO

Arm description:

Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized at Week 24 to receive 30 mg apremilast twice daily during the active treatment phase.

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 twice a day.

Number of subjects in period 2[4]	Apremilast 20 mg	Apremilast 30 mg	Placebo / Apremilast 20 mg EE
Started	137	134	43
Completed	125	114	35
Not completed	12	20	8
Consent withdrawn by subject	3	7	3
Adverse event, non-fatal	2	3	1
Non-compliance with study drug	-	2	-

Unspecified	1	1	-
Lost to follow-up	1	-	-
Lack of efficacy	5	7	4

Number of subjects in period 2[4]	Placebo / Apremilast 20 mg XO	Placebo / Apremilast 30 mg EE	Placebo / Apremilast 30 mg XO
Started	27	41	28
Completed	25	34	28
Not completed	2	7	0
Consent withdrawn by subject	1	3	-
Adverse event, non-fatal	-	2	-
Non-compliance with study drug	-	-	-
Unspecified	-	-	-
Lost to follow-up	1	-	-
Lack of efficacy	-	2	-

Notes:

[4] - 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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

Period 3

Period 3 title	Long-Term Safety Phase (Year 2)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily in the active treatment/long-term safety phase (LTSP).

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

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 twice daily.

Arm title	Placebo/Apremilast 20 mg

Arm description:

Participants initially randomized to placebo tablets twice daily in the 24-week placebo controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 continued receiving apremilast 20 mg BID in the active treatment / long-term safety phase.

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 20 mg tablets twice daily.

Arm title	Placebo/Apremilast 30 mg

Arm description:

Participants initially randomized to placebo tablets BID in the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued receiving apremilast 30 mg BID in the active treatment / long-term safety phase.

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 twice daily.

Number of subjects in period 3[5]	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg
Started	119	109	58
Completed	107	95	48
Not completed	12	14	10
Consent withdrawn by subject	7	9	4
Adverse event, non-fatal	1	1	2
Miscellaneous	-	-	-
Lost to follow-up	-	2	-
Lack of efficacy	4	2	4

Number of subjects in period 3[5]	Placebo/Apremilast 30 mg

Started	60
Completed	51
Not completed	9
Consent withdrawn by subject	6
Adverse event, non-fatal	2
Miscellaneous	1
Lost to follow-up	-
Lack of efficacy	-

Notes:

[5] - 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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

Period 4

Period 4 title	Long-Term Safety Phase (Year 3)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment / long-term safety phase.

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

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 twice daily.

Arm title	Placebo/Apremilast 20 mg

Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase.

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 20 mg tablets twice daily.

Arm title	Placebo/Apremilast 30 mg

Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily the active treatment / long-term safety phase.

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 twice daily.

Number of subjects in period 4	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg
Started	107	95	48
Completed	89	84	42
Not completed	18	11	6
Consent withdrawn by subject	5	1	1
Adverse event, non-fatal	4	1	2
Miscellaneous	-	3	-
Non-compliance with study drug	-	1	-
Lost to follow-up	-	-	-
Lack of efficacy	8	5	3
Protocol deviation	1	-	-

Number of subjects in period 4	Placebo/Apremilast 30 mg
Started	51
Completed	46
Not completed	5
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Miscellaneous	2

Non-compliance with study drug	-
Lost to follow-up	1
Lack of efficacy	1
Protocol deviation	-

Period 5

Period 5 title	Long-Term Safety Phase (Year 4)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment/long-term safety phase.

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

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 twice daily.

Arm title	Placebo/Apremilast 20 mg

Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase.

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 20 mg tablets twice daily

Arm title	Placebo/Apremilast 30 mg

Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily in the active treatment / long-term safety phase.

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 twice daily

Number of subjects in period 5[6]	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg
Started	89	84	41
Completed	80	77	37
Not completed	9	7	4
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	4	2	1
Adverse event, non-fatal	1	2	1
Miscellaneous	2	-	-
Lost to follow-up	-	-	1
Lack of efficacy	2	2	1

Number of subjects in period 5[6]	Placebo/Apremilast 30 mg
Started	46
Completed	39
Not completed	7
Adverse event, serious fatal	1
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Miscellaneous	1
Lost to follow-up	-
Lack of efficacy	1

Notes:

[6] - 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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

Period 6

Period 6 title	Long-Term Safety Phase (Year 5)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment/long-term safety phase. (After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to 30 mg apremilast BID dose).

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 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

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 twice daily.

Arm title	Placebo/Apremilast 20 mg

Arm description:

Participants initially randomized to placebo tablets BID during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase. After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose.

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 20 mg tablets twice daily.

Arm title	Placebo/Apremilast 30 mg

Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily in the active treatment / long-term safety phase.

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 twice daily

Number of subjects in period 6	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg
Started	80	77	37
Completed	72	69	33
Not completed	8	8	5
Consent withdrawn by subject	3	3	1
Adverse event, non-fatal	2	2	2
Miscellaneous	1	1	-
Non-compliance with study drug	1	-	-
Lack of efficacy	1	2	2
Joined	0	0	1
1 subject not counted in Year 5	-	-	1

Number of subjects in period 6	Placebo/Apremilast 30 mg
Started	39
Completed	37
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Miscellaneous	-
Non-compliance with study drug	-
Lack of efficacy	1
Joined	0
1 subject not counted in Year 5	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants initially randomized to placebo tablets twice daily (BID) in the 24-week placebo-controlled phase. Participants who did not have at least 20% improvement in swollen and tender joint counts at Week (Wk) 16 were re-randomized to either 20 mg or 30 mg apremilast twice daily [(early escape (EE)].	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	

Reporting group values	Placebo	Apremilast 20 mg	Apremilast 30 mg
Number of subjects	162	163	163
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)	146	149	145
From 65-84 years	16	14	18
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.2	50.9	50.5
standard deviation	± 10.97	± 11.82	± 11.20
Gender, Male/Female Units: Subjects			
Female	87	95	95
Male	75	68	68
Duration of Psoriatic Arthritis Units: years			
arithmetic mean	7.76	7.83	6.82
standard deviation	± 8.254	± 8.621	± 7.592

Reporting group values	Total		
Number of subjects	488		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	440		
From 65-84 years	48		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	277		
Male	211		
Duration of Psoriatic Arthritis			
Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants initially randomized to placebo tablets twice daily (BID) in the 24-week placebo-controlled phase. Participants who did not have at least 20% improvement in swollen and tender joint counts at Week (Wk) 16 were re-randomized to either 20 mg or 30 mg apremilast twice daily [(early escape (EE)].	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily in the active treatment/long-term safety phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.	
Reporting group title	Placebo / Apremilast 20 mg EE
Reporting group description:	
Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized due to early escape (EE) at Week 16 to receive 20 mg apremilast twice daily during the active treatment phase.	
Reporting group title	Placebo / Apremilast 20 mg XO
Reporting group description:	
Participants initially randomized to receive placebo twice daily in the 24-week placebo-controlled phase were re-randomized at Week 24 (XO) to receive 20 mg apremilast twice daily during the active treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg EE
Reporting group description:	
Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized due to early escape (EE) at Week 16 to receive 30 mg apremilast twice daily during the active treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg XO
Reporting group description:	
Participants initially randomized to placebo twice daily in the 24-week placebo-controlled phase were re-randomized at Week 24 to receive 30 mg apremilast twice daily during the active treatment phase.	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily in the active treatment/long-term safety phase (LTSP).	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.	

Reporting group title	Placebo/Apremilast 20 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily in the 24-week placebo controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 continued receiving apremilast 20 mg BID in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 30 mg

Reporting group description:

Participants initially randomized to placebo tablets BID in the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued receiving apremilast 30 mg BID in the active treatment / long-term safety phase.

Reporting group title	Apremilast 20 mg

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment / long-term safety phase.

Reporting group title	Apremilast 30 mg

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 30 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily the active treatment / long-term safety phase.

Reporting group title	Apremilast 20 mg

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment/long-term safety phase.

Reporting group title	Apremilast 30 mg

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 30 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily in the active treatment / long-term safety phase.

Reporting group title	Apremilast 20 mg

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment/long-term safety phase. (After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to 30 mg apremilast BID dose).

Reporting group title	Apremilast 30 mg

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-

controlled phase continued to receive 30 mg apremilast tablets twice daily in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg

Reporting group description:

Participants initially randomized to placebo tablets BID during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg twice daily in the active treatment / long-term safety phase. After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose.

Reporting group title	Placebo/Apremilast 30 mg

Reporting group description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 30 mg twice daily in the active treatment / long-term safety phase.

Subject analysis set title	Placebo /Apremilast 20 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects initially randomized to placebo tablets BID during the 24-week placebo-controlled phase were re-randomized to apremilast 20 mg twice daily at Week 16 or Week 24 and continued receiving apremilast 20 mg BID in the active treatment / long-term safety phase.

Subject analysis set title	Placebo/Apremilast 30 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects initially randomized to placebo tablets BID during the 24-week placebo-controlled phase were re-randomized to apremilast 30 mg twice daily at Week 16 or Week 24 and continued receiving apremilast 30 mg BID in the active treatment / long-term safety phase.

Subject analysis set title	Apremilast 20 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued receiving 20 mg Apremilast twice daily in the active treatment/long-term safety phase.

Subject analysis set title	Apremilast 30 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued receiving 30 mg apremilast twice daily in the active treatment/long-term safety phase.

Subject analysis set title	Apremilast 20 mg (Pre-switch)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received apremilast 20 mg BID, regardless of when the apremilast exposure started (at Week 0, 16, or 24). Only the TEAEs that occurred during apremilast 20 mg BID treatment (before the switch to 30 mg apremilast) were included.

Subject analysis set title	Apremilast 20 mg/30 mg (Post-switch)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who switched from apremilast 20 mg BID to apremilast 30 mg BID. Only the TEAEs that occurred during APR 30 mg BID treatment were included.

Subject analysis set title	Apremilast 30 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received apremilast 30 mg BID regardless of when their apremilast-exposure started (at Weeks 0, 16, or 24).

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

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

End point description:

Percentage of participants with a ACR 20 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: ◦Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); ◦Patient's global assessment of disease activity (measured on a 100 mm VAS); ◦Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); ◦C-Reactive Protein. Full analysis set (FAS) = subjects randomized as specified per protocol; subjects who were randomized in error and did not receive any dose of study drug were excluded. Subjects who withdrew early who did not have sufficient data for a determination of response status at Week 16 were counted as non-responders

End point type	Primary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	18.9	37.4	32.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

In order to maintain the Type 1 error at the 0.05 significance level, the Hochberg procedure was to be used. The results of the endpoint were to be considered statistically significant if both the 30 mg apremilast dose versus placebo comparison and the 20 mg versus placebo comparison were statistically significant at the 0.05 significance level, or one of the comparisons was statistically significant at the 0.025 level.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.006 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	22.7

Notes:

[1] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% confidence interval (CI) is based on a normal approximation to the weighted average.

[2] - 2-sided p-value is based on the Cochran-Mantel-Haenszel (CMH) test adjusting for baseline disease modifying antirheumatic drug (DMARD) use.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

In order to maintain the Type 1 error at the 0.05 significance level, the Hochberg procedure was to be used. The results of the endpoint were to be considered statistically significant if both the 30 mg apremilast dose versus placebo comparison and the 20 mg versus placebo comparison were statistically significant at the 0.05 significance level, or one of the comparisons was statistically significant at the 0.025 level.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.1
upper limit	28.2

Notes:

[3] - 2-sided p-value is based on the CMH test adjusting for baseline DMARD 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:

The Health Assessment Questionnaire - Disability Index 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. Negative mean changes from Baseline in the overall score indicate improvement in functional ability. FAS; participants with a baseline value and at least 1 post-baseline value at or prior to Week 16 are included; Last observation carried forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	159	154	
Units: units on a scale				
least squares mean (standard error)	-0.053 (± 0.0358)	-0.157 (± 0.0351)	-0.193 (± 0.0354)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Pairwise comparisons (30 mg vs placebo and 20 mg vs placebo) were conducted conditional on the primary endpoint results. If the primary endpoint was statistically significant for both apremilast dose groups, pairwise comparisons for the HAQ-DI were to be evaluated at the 0.05 level using the Hochberg procedure. If only one apremilast dose was statistically significant, then only the comparison between that apremilast dose and placebo was conducted for the HAQ-DI score, at the 0.025 level.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.236
upper limit	-0.045

Notes:

[4] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Pairwise comparisons (30 mg vs placebo and 20 mg vs placebo) were conducted conditional on the primary endpoint results. If the primary endpoint was statistically significant for both apremilast dose groups, pairwise comparisons for the HAQ-DI were to be evaluated at the 0.05 level using the Hochberg procedure. If only one apremilast dose was statistically significant, then only the comparison between that apremilast dose and placebo was conducted for the HAQ-DI score, at the 0.025 level.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.104

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	-0.009

Notes:

[5] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Percentage of Participants with an ACR 20 Response at Week 24

End point title	Percentage of Participants with an ACR 20 Response 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: ◦Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); ◦Patient's global assessment of disease activity (measured on a 100 mm VAS); ◦Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); ◦C-Reactive Protein. FAS population; subjects who discontinued early, escaped early at Week 16 or who did not have sufficient data for a definitive determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	15.7	31.3	24.7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0394 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	9.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	17.8

Notes:

[6] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.
[7] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0009 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	24.7

Notes:

[8] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.
[9] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD 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:

The Health Assessment Questionnaire - Disability Index 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. Negative mean changes from Baseline in the overall score indicate improvement in functional ability. FAS population. subjects with a baseline value and at least 1 post-baseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	159	154	
Units: units on a scale				
least squares mean (standard error)	-0.085 (± 0.0377)	-0.165 (± 0.0370)	-0.206 (± 0.0372)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0191 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.222
upper limit	-0.02

Notes:

[10] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.
[11] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.1179 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.02

Notes:

[12] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.
[13] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

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

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

End point description:

The Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) 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 post-baseline value at or prior to Week 16 are included; LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	159	153	
Units: units on a scale				
least squares mean (standard error)	0.81 (± 0.678)	2.17 (± 0.664)	2.91 (± 0.671)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.0237 [15]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	3.92

Notes:

[14] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.

[15] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.1388 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	3.15

Notes:

[16] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above.
[17] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Percentage of Participants with a Modified Psoriatic Arthritis Response Criteria (PsARC) Response at Week 16

End point title	Percentage of Participants with a Modified Psoriatic Arthritis Response Criteria (PsARC) Response at Week 16

End point description:

Modified PsARC response is defined as improvement in at least 2 of the 4 measures, at least one of which must be tender joint count or swollen joint count, and no worsening in any of the 4 measures: - 78 tender joint count, - 76 swollen joint count, - Patient global assessment of disease activity, measured on a 100 mm visual Analog scale (VAS), where 0 mm = lowest disease activity and 100 mm = highest; - Physician global assessment of disease activity, measured on a 100 mm VAS, where 0 mm = lowest disease activity and 100 mm = highest. Improvement or worsening in joint counts is defined as decrease or increase, respectively, from baseline by ≥ 30%, and improvement or worsening in global assessments is defined as decrease or increase, respectively, from baseline by ≥ 20 mm VAS. Full analysis set; Participants who discontinued early, or 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	33.3	47.9	48.1	

Statistical analyses

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

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0065 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	25.5

Notes:

[18] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above. Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[19] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0071 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	25.2

Notes:

[20] - Secondary endpoints from the placebo-controlled period (Weeks 16 and 24) were analyzed in a hierarchical fashion to control the Type I error rate as described above. Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[21] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Change from Baseline in Patient’s Assessment of Pain at Week 16

End point title	Change from Baseline in Patient’s Assessment of Pain at Week 16

End point description:

The participant was asked to place a vertical line on a 100-mm visual analog scale on which the left-hand boundary (score = 0 mm) represents “no pain,” and the right-hand boundary (score = 100 mm) represents “pain as severe as can be imagined.” The distance from the mark to the left-hand boundary was recorded in millimeters. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included; LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	157	152	
Units: mm				
least squares mean (standard error)	-7.0 (± 1.93)	-12.5 (± 1.89)	-11.9 (± 1.90)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0648 [22]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	0.3

Notes:

[22] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0347 [23]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-0.4

Notes:

[23] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change from Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 16

End point title	Change from Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 16

End point description:

The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 (i.e., pre-existing enthesopathy) and at least 1 postbaseline value at or prior to Week 16 are included; LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	105	97	
Units: units on a scale				
least squares mean (standard error)	-1.0 (± 0.29)	-0.9 (± 0.28)	-1.4 (± 0.29)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3496 [24]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.4

Notes:

[24] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8874 [25]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.8

Notes:

[25] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change from Baseline in Dactylitis Severity Score at Week 16

End point title	Change from Baseline in Dactylitis Severity Score at Week 16

End point description:

Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet will be rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set. Participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) and at least 1 postbaseline value at or prior to Week 16 are included. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	75	70	
Units: units on a scale				
least squares mean (standard error)	-1.1 (± 0.28)	-0.8 (± 0.26)	-1.3 (± 0.26)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5438 [26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.5

Notes:

[26] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3759 [27]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1

Notes:

[27] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 16

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 16

End point description:

The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the: - 28 tender joint count (TJC), - 28 swollen joint count (SJC), - Patient's Global Assessment of Disease Activity measured on a 10 cm visual analog scale (VAS), where 0 cm = lowest disease activity and 10 cm = highest; - Physician's Global Assessment of Disease Activity -measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest. The CDAI score ranges from 0-76 where lower scores indicate less disease activity. The following thresholds of disease activity have been defined for the CDAI: Remission: ≤ 2.8 Low Disease Activity: > 2.8 and ≤ 10 Moderate Disease Activity: > 10 and ≤ 22 High Disease Activity: > 22. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	155	146	
Units: units on a scale				
least squares mean (standard error)	-3.30 (± 0.871)	-7.75 (± 0.851)	-6.81 (± 0.869)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 [28]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	-1.16

Notes:

[28] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [29]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.76
upper limit	-2.14

Notes:

[29] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

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

End point title	Change from Baseline in the Disease Activity Score (DAS28) 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 distal interphalangeal (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 approximately 10, with the upper bound dependent on the highest possible level of CRP. 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. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	156	151	
Units: units on a scale				
least squares mean (standard error)	-0.27 (± 0.082)	-0.74 (± 0.080)	-0.67 (± 0.080)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [30]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.18

Notes:

[30] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.25

Notes:

[31] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate

Secondary: Change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score at Week 16

End point title	Change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score at Week 16

End point description:

The FACIT-Fatigue scale is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The FACIT-Fatigue scale score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. A positive change from baseline score indicates an improvement. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	157	154	
Units: units on a scale				
least squares mean (standard error)	0.63 (± 0.724)	0.91 (± 0.712)	2.75 (± 0.715)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7803 [32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	2.2

Notes:

[32] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

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

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0318 [33]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	4.06

Notes:

[33] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in 36-item Short Form Health Survey (SF-36) Physical Functioning Domain at Week 24

End point title	Change From Baseline in 36-item Short Form Health Survey (SF-36) Physical Functioning Domain at Week 24

End point description:

The Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) 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 post-baseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	159	154	
Units: units on a scale				
least squares mean (standard error)	1.44 (± 0.688)	2.97 (± 0.673)	3.30 (± 0.679)	

Statistical analyses

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

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0473 [34]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	3.7

Notes:

[34] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0997 [35]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	3.35

Notes:

[35] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Percentage of Participants With a Modified Psoriatic Arthritis Response Criteria (PsARC) Response at Week 24

End point title	Percentage of Participants With a Modified Psoriatic Arthritis Response Criteria (PsARC) Response at Week 24

End point description:

Modified PsARC response is defined as improvement in at least 2 of the 4 measures, at least one of which must be tender joint count or swollen joint count, and no worsening in any of the 4 measures: • 78 tender joint count, • 76 swollen joint count, • Patient global assessment of disease activity, measured on a 100 mm visual Analog scale (VAS), where 0 mm = lowest disease activity and 100 mm = highest; • Physician global assessment of disease activity, measured on a 100 mm VAS, where 0 mm = lowest disease activity and 100 mm = highest. Improvement or worsening in joint counts is defined as decrease or increase, respectively, from baseline by ≥ 30%, and improvement or worsening in global assessments is defined as decrease or increase, respectively, from baseline by ≥ 20 mm VAS. Full analysis set; Participants who discontinued early, escaped early at Week 16 or who did not have sufficient data for a definitive determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	24.5	39.9	32.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.1195 [37]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	17.5

Notes:

[36] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights.

[37] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.0026 [39]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	25.5

Notes:

[38] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights

[39] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Change From Baseline in Patient's Assessment of Pain at Week 24

End point title	Change From Baseline in Patient's Assessment of Pain at Week 24

End point description:

The participant was asked to place a vertical line on a 100-mm visual analog scale on which the left-hand boundary (score = 0 mm) represents "no pain," and the right-hand boundary (score = 100 mm) represents "pain as severe as can be imagined." The distance from the mark to the left-hand boundary was recorded in millimeters. Full analysis set; participants with a baseline value and at least 1 post-baseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	158	153	
Units: mm				
least squares mean (standard error)	-8.0 (± 1.90)	-11.5 (± 1.86)	-9.7 (± 1.88)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5067 [40]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	3.4

Notes:

[40] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1762 [41]
Method	ANCOVA
Parameter estimate	LS mean Difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	1.6

Notes:

[41] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 24

End point title	Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 24

End point description:

The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 (i.e., pre-existing enthesopathy) and at least 1 post-baseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	105	98	
Units: units on a scale				
least squares mean (standard error)	-0.9 (± 0.29)	-0.9 (± 0.28)	-1.3 (± 0.29)	

Statistical analyses

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

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2719 [42]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.3

Notes:

[42] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9727 [43]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.7

Notes:

[43] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in Dactylitis Severity Score at Week 24

End point title	Change From Baseline in Dactylitis Severity Score at Week 24

End point description:

Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet will be rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set. Participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) and at least 1 postbaseline value at or prior to Week 24 are included. LOCF was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	75	71	
Units: units on a scale				
least squares mean (standard error)	-1.1 (± 0.27)	-0.9 (± 0.25)	-1.4 (± 0.26)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6777 [44]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.8

Notes:

[44] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3705 [45]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.4

Notes:

[45] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24

End point description:

The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the: • 28

tender joint count (TJC), • 28 swollen joint count (SJC), • Patient's Global Assessment of Disease Activity measured on a 10 cm visual analog scale (VAS), where 0 cm = lowest disease activity and 10 cm = highest; • Physician's Global Assessment of Disease Activity -measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest. The CDAI score ranges from 0-76 where lower scores indicate less disease activity. The following thresholds of disease activity have been defined for the CDAI: Remission: ≤ 2.8; Low Disease Activity: > 2.8 and ≤ 10; Moderate Disease Activity: > 10 and ≤ 22; High Disease Activity: > 22. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	155	148	
Units: units on a scale				
least squares mean (standard error)	-3.21 (± 0.884)	-7.71 (± 0.864)	-6.35 (± 0.878)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097 [46]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.52
upper limit	-0.76

Notes:

[46] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [47]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.85
upper limit	-2.16

Notes:

[47] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in the Disease Activity Score (DAS28) at Week 24

End point title	Change From Baseline in the Disease Activity Score (DAS28) 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 approximately 10, with the upper bound dependent on the highest possible level of CRP. 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. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	157	152	
Units: units on a scale				
least squares mean (standard error)	-0.27 (± 0.084)	-0.73 (± 0.082)	-0.65 (± 0.083)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [48]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.15

Notes:

[48] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [49]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.23

Notes:

[49] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Change From Baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score at Week 24

End point title	Change From Baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Score at Week 24

End point description:

The FACIT-Fatigue scale is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The FACIT-Fatigue scale score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. A positive change from baseline score indicates an improvement. Full analysis set; participants with a baseline value and at least 1 postbaseline value at or prior to Week 24 are included; LOCF imputation was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	157	154	
Units: units on a scale				
least squares mean (standard error)	0.52 (± 0.721)	0.68 (± 0.710)	2.65 (± 0.713)	

Statistical analyses

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

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0303 [50]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	4.07

Notes:

[50] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8704 [51]
Method	ANCOVA
Parameter estimate	LS mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	2.08

Notes:

[51] - Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

Secondary: Percentage of Participants with MASES Improvement ≥ 20% at Week 16

End point title	Percentage of Participants with MASES Improvement ≥ 20% at Week 16

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improved by ≥ 20% from Baseline after 16 weeks of treatment. The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 (i.e., pre-existing enthesopathy) are included; LOCF was used. Participants who did not have sufficient data (observed or imputed) for a 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	107	101	
Units: percentage of participants				
number (not applicable)	52.9	54.2	56.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.8462 [53]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	14.7

Notes:

[52] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights.
[53] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.6022 [55]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	17.2

Notes:

[54] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights.
[55] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use

Secondary: Percentage of Participants with Dactylitis improvement ≥ 1 point at Week 16

End point title	Percentage of Participants with Dactylitis improvement ≥ 1 point at Week 16

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 16 weeks of treatment. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set; participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) are included; LOCF was used. Participants who did not have sufficient data (observed or imputed) for a 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	77	73	
Units: percentage of participants				
number (not applicable)	59.1	62.3	61.6	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.7337 [57]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	18.9

Notes:

[56] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[57] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.6881 [59]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	19.3

Notes:

[58] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[59] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with Good or Moderate European League Against Rheumatism (EULAR) Response at Week 16

End point title	Percentage of Participants with Good or Moderate European League Against Rheumatism (EULAR) Response at Week 16

End point description:

A EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS-28 score. A Good Response is defined as an improvement (decrease) in the DAS28 of more than 1.2 compared with Baseline and attainment of a DAS28 score less than or equal to 3.2. A Moderate Response is defined as either: • an improvement (decrease) in the DAS28 of greater than 0.6 and less than or equal to 1.2 and attainment of a DAS28 score of less than or equal to 5.1 or, • an improvement (decrease) in the DAS28 of more than 1.2 and attainment of a DAS28 score of greater than 3.2. Full analysis set; Participants who discontinued early, or 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	31.4	53.4	48.8	

Statistical analyses

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

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.0014 [61]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	17.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	27.9

Notes:

[60] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[61] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.0001 [63]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	22.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	32.5

Notes:

[62] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[63] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with MASES Improvement ≥ 20% at Week 24

End point title	Percentage of Participants with MASES Improvement ≥ 20% at Week 24

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improved by ≥ 20% from Baseline after 24 weeks of treatment. The MASES score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. FAS; participants with a baseline MASES > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for participants who EE at Week 16. Participants who did not have sufficient data for a determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	107	101	
Units: percentage of participants				
number (not applicable)	51.0	57.0	57.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.3376 [65]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	20

Notes:

[64] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[65] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.3756 [67]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	19.4

Notes:

[66] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[67] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with Dactylitis improvement ≥ 1 point at Week 24

End point title	Percentage of Participants with Dactylitis improvement ≥ 1 point at Week 24

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 24 weeks of treatment. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set; participants with a baseline dactylitis severity score > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16. Participants who did not have sufficient data (observed or imputed) for a determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	77	73	
Units: percentage of participants				
number (not applicable)	62.1	68.8	68.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.3959 [69]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	22.2

Notes:

[68] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[69] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.3941 [71]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	22.4

Notes:

[70] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran-Mantel-Haenszel (CMH) weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[71] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with Good or Moderate EULAR response at Week 24

End point title	Percentage of Participants with Good or Moderate EULAR response at Week 24

End point description:

EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS-28 score. A Good Response is defined as an improvement (decrease) in the DAS28 of more than 1.2 compared with Baseline and attainment of a DAS28 score less than or equal to 3.2. A Moderate Response is defined as either: • an improvement (decrease) in the DAS28 of greater than 0.6 and less than or equal to 1.2 and attainment of a DAS28 score of less than or equal to 5.1 or, • an improvement (decrease) in the DAS28 of more than 1.2 and attainment of a DAS28 score of greater than 3.2. Full analysis set; Participants who discontinued early, escaped early at Week 16 or who did not have sufficient data for a definitive determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	21.4	41.7	33.3	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.0001 [73]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	20.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.8
upper limit	30.3

Notes:

[72] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[73] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.0142 [75]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	21.7

Notes:

[74] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[75] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with a ACR 50 Response at Week 16

End point title	Percentage of Participants with a ACR 50 Response at Week 16

End point description:

Percentage of participants with an American College of Rheumatology 50% (ACR50) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 50% improvement in 78 tender joint count; • ≥ 50% improvement in 76 swollen joint count; and • ≥ 50% improvement in at least 3 of the 5 following parameters: o Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); o Patient's global assessment of disease activity (measured on a 100 mm VAS); o Physician's global assessment of disease activity (measured on a 100 mm VAS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); o C-Reactive Protein. Full analysis set; Participants who discontinued early, or 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	5.0	14.7	10.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.0589 [77]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	11.3

Notes:

[76] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[77] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.0034 [79]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	16.1

Notes:

[78] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[79] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with an ACR 70 Response at Week 16

End point title	Percentage of Participants with an ACR 70 Response at Week 16

End point description:

Percentage of participants with an American College of Rheumatology 70% (ACR70) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 70% improvement in 78 tender joint count; • ≥ 70% improvement in 76 swollen joint count; and • ≥ 70% improvement in at least 3 of the 5 following parameters: o Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); o Patient's global assessment of disease activity (measured on a 100 mm VAS); o Physician's global assessment of disease activity (measured on a 100 mm VAS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); o C-Reactive Protein. Full analysis set; Participants who discontinued early, or 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 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	0.6	3.7	1.2	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.562 [81]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.7

Notes:

[80] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[81] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 0.057 [83]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	6.2

Notes:

[82] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[83] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with an ACR 50 Response at Week 24

End point title	Percentage of Participants with an ACR 50 Response at Week 24

End point description:

Percentage of participants with an American College of Rheumatology 50% (ACR50) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 50% improvement in 78 tender joint count; • ≥ 50% improvement in 76 swollen joint count; and • ≥ 50% improvement in at least 3 of the 5 following parameters: o Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); o Patient's global assessment of disease activity (measured on a 100 mm VAS); o Physician's global assessment of disease activity (measured on a 100 mm VAS); o Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); o C-Reactive Protein. Full analysis set; Participants who discontinued early, escaped early at Week 16 or who did not have sufficient data for a definitive determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	8.8	14.1	11.7	

Statistical analyses

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

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.3629 [85]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	9.6

Notes:

[84] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[85] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 0.1323 [87]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	12.3

Notes:

[86] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[87] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with a ACR 70 Response at Week 24

End point title	Percentage of Participants with a ACR 70 Response at Week 24

End point description:

Percentage of participants with an American College of Rheumatology 70% (ACR70) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 70% improvement in 78 tender joint count; • ≥ 70% improvement in 76 swollen joint count; and • ≥ 70% improvement in at least 3 of the 5 following parameters: ◦ Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); ◦ Patient's global assessment of disease activity (measured on a 100 mm VAS); ◦ Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦ Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); ◦C-Reactive Protein. Full analysis set; Participants who discontinued early, escaped early at Week 16 or who did not have sufficient data for a definitive determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: percentage of participants				
number (not applicable)	3.1	5.5	2.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	= 0.2929 [89]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	6.8

Notes:

[88] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[89] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[90]
P-value	= 0.7273 [91]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	3

Notes:

[90] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[91] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants Achieving a MASES Score of Zero at Week 16

End point title	Percentage of Participants Achieving a MASES Score of Zero at Week 16

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improves to 0 after 16 weeks of treatment. The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 (i.e., pre-existing enthesopathy) are included; LOCF was used. Participants who did not have sufficient data (observed or imputed) for a determination of response status at Week 16 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	107	101	
Units: percentage of participants				
number (not applicable)	23.1	29.0	20.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[92]
P-value	= 0.7023 [93]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	9.1

Notes:

[92] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[93] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[94]
P-value	= 0.3305 [95]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	17.7

Notes:

[94] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[95] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants Achieving a Dactylitis Score of Zero at Week 16

End point title	Percentage of Participants Achieving a Dactylitis Score of Zero at Week 16

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improves to zero after 16 weeks of treatment. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set; participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) are included; LOCF was used. Participants who did not have sufficient data (observed or imputed) for a determination of response status at Week 16 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	77	73	
Units: percentage of participants				
number (not applicable)	40.9	42.9	41.1	

Statistical analyses

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

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	= 0.9698 [97]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	16.6

Notes:

[96] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[97] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[98]
P-value	= 0.8205 [99]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	18.1

Notes:

[98] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[99] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants Achieving a MASES Score of Zero at Week 24

End point title	Percentage of Participants Achieving a MASES Score of Zero at Week 24

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improves to 0 after 24 weeks of treatment. The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16. Participants who did not have sufficient data for a determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	107	101	
Units: percentage of participants				
number (not applicable)	24.0	29.9	22.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[100]
P-value	= 0.8424 [101]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	10.3

Notes:

[100] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[101] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[102]
P-value	= 0.3395 [103]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	17.8

Notes:

[102] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[103] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use

Secondary: Percentage of Participants Achieving a Dactylitis Score of Zero at Week 24

End point title	Percentage of Participants Achieving a Dactylitis Score of Zero at Week 24

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improves to zero after 24 weeks of treatment. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Full analysis set; participants with a baseline dactylitis severity score > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16. Participants who did not have sufficient data for a determination of response status at Week 24 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	59	68	
Units: percentage of participants				
number (not applicable)	40.9	44.2	46.6	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[104]
P-value	= 0.4811 [105]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	22.1

Notes:

[104] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[105] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[106]
P-value	= 0.6965 [107]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	19.5

Notes:

[106] - Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.
[107] - The 2-sided p-value is based on the CMH test adjusting for baseline DMARD use.

Secondary: Percentage of Participants with a ACR 20 Response at Week 52

End point title	Percentage of Participants with a ACR 20 Response at Week 52

End point description:

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: ◦Patient's assessment of pain (measured on a 100 mm VAS); ◦Patient's global assessment of disease activity (measured on a 100 mm VAS; ◦Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦Patient's self-assessment of physical function; ◦C-Reactive Protein.
Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population consists of all participants who were randomized or re-randomized to apremilast at any time during the study; only those who had sufficient data for a definitive determination of response at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	61	121	116
Units: percentage of participants				
number (confidence interval 95%)	53.3 (40.0 to 63.3)	47.5 (34.6 to 60.7)	52.9 (43.6 to 62.0)	52.6 (43.1 to 61.9)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The 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. Negative mean changes from Baseline in the overall score indicate improvement in functional ability. Apremilast Subjects as Randomized/Re-randomized (AAR) Population consisted of subjetcs who were randomized or re-randomized to apremilast at any time during the study. Only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	63	125	117
Units: units on a scale				
arithmetic mean (standard deviation)	-0.208 (± 0.4831)	-0.310 (± 0.5990)	-0.192 (± 0.5729)	-0.330 (± 0.5089)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the SF-36 Physical Functioning Scale Score at Week 52

End point title	Change from Baseline in the SF-36 Physical Functioning Scale Score at Week 52

End point description:

The Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) 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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a Baseline value and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	63	124	115
Units: units on a scale				
arithmetic mean (standard deviation)	4.13 (± 9.106)	5.97 (± 9.612)	4.05 (± 8.752)	4.97 (± 9.656)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Modified PsARC Response at Week 52

End point title	Percentage of Participants with a Modified PsARC Response at Week 52

End point description:

Modified PsARC response is defined as improvement in at least 2 of the 4 measures, at least one of which must be tender joint count or swollen joint count, and no worsening in any of the 4 measures: • 78 tender joint count, • 76 swollen joint count, • Patient global assessment of disease activity, measured on a 100 mm VAS, where 0 mm = lowest disease activity and 100 mm = highest; • Physician global assessment of disease activity, measured on a 100 mm VAS, where 0 mm = lowest disease activity and 100 mm = highest. Improvement or worsening in joint counts = a decrease or increase, respectively, from baseline by ≥ 30%, and improvement or worsening in global assessments = a decrease or increase, from baseline by ≥ 20 mm VAS. 2 sided 95% confidence interval is based on the Clopper-Pearson method. Apremilast Subjects as Randomized/Re-randomized (AAR) population; only subjects who had sufficient data for a definitive response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	123	114
Units: percentage of participants				
number (confidence interval 95%)	78.3 (65.8 to 87.9)	73.3 (60.3 to 83.9)	72.4 (63.6 to 80.0)	74.6 (65.6 to 82.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Patient Assessment of Pain at Week 52

End point title	Change from Baseline in the Patient Assessment of Pain at Week 52

End point description:

The participant was asked to place a vertical line on a 100-mm visual analog scale on which the left-hand boundary (score = 0 mm) represents "no pain," and the right-hand boundary (score = 100 mm)

represents "pain as severe as can be imagined." The distance from the mark to the left-hand boundary was recorded in millimeters. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a Baseline value and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	62	125	117
Units: mm				
arithmetic mean (standard deviation)	-15.6 (± 23.77)	-16.0 (± 24.48)	-13.5 (± 27.78)	-12.9 (± 26.54)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 52

End point title	Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES) at Week 52

End point description:

The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value > 0 (i.e., pre-existing enthesopathy) and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	39	80	78
Units: units on a scale				
arithmetic mean (standard deviation)	-2.5 (± 4.41)	-2.5 (± 2.73)	-1.7 (± 3.12)	-2.1 (± 2.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Dactylitis Severity Score at Week 52

End point title	Change from Baseline in the Dactylitis Severity Score at Week 52

End point description:

Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet will be rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value > 0 (i.e., pre-existing dactylitis) and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	27	57	60
Units: units on a scale				
arithmetic mean (standard deviation)	-1.9 (± 1.14)	-2.1 (± 2.32)	-1.8 (± 1.98)	-1.8 (± 2.06)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the CDAI Score at Week 52

End point title	Change from Baseline in the CDAI Score at Week 52

End point description:

The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the: • 28 tender joint count (TJC), • 28 swollen joint count (SJC), • Patient's Global Assessment of Disease Activity measured on a 10 cm visual analog scale (VAS), where 0 cm = lowest disease activity and 10 cm = highest; • Physician's Global Assessment of Disease Activity -measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest. The CDAI score ranges from 0-76 where lower scores indicate less disease activity. The following thresholds of disease activity have been defined for the CDAI: Remission: ≤ 2.8 Low Disease Activity: > 2.8 and ≤ 10 Moderate Disease Activity: > 10 and ≤ 22 High Disease Activity: > 22. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	123	114
Units: units on a scale				
arithmetic mean (standard deviation)	-13.66 (± 9.811)	-13.13 (± 13.148)	-12.03 (± 10.492)	-14.38 (± 11.531)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the DAS28 at Week 52

End point title	Change from baseline in the DAS28 at Week 52

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 approximately 10, with the upper bound dependent on the highest possible level of CRP. 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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a Baseline value and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	62	125	117
Units: units on a scale				
arithmetic mean (standard deviation)	-1.18 (± 1.015)	-1.18 (± 1.366)	-1.11 (± 1.059)	-1.30 (± 1.033)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACIT-Fatigue Scale Score at Week 52

End point title	Change from Baseline in the FACIT-Fatigue Scale Score at Week 52

End point description:

The FACIT-Fatigue scale is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The FACIT-Fatigue scale score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. A positive change from baseline score indicates an improvement.

The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value and a Week 52 value are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	59	63	123	115
Units: units on a scale				
arithmetic mean (standard deviation)	1.97 (± 8.544)	4.95 (± 9.414)	2.45 (± 9.481)	4.38 (± 9.847)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With MASES Improvement ≥ 20% at Week 52

End point title	Percentage of Participants With MASES Improvement ≥ 20% at Week 52

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improved by ≥ 20% from Baseline after 52 weeks. The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants with a baseline MASES > 0 and who had sufficient data for a definitive response at Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	39	80	78
Units: percentage of participants				
number (confidence interval 95%)	72.5 (56.1 to 85.4)	79.5 (63.5 to 90.7)	70.0 (58.7 to 79.7)	69.2 (57.8 to 79.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Dactylitis Improvement ≥ 1 Point at Week 52

End point title	Percentage of Participants With Dactylitis Improvement ≥ 1 Point at Week 52

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 52 weeks. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; Participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) and who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	27	57	60
Units: percentage of participants				
number (confidence interval 95%)	95.7 (78.1 to 99.9)	88.9 (70.8 to 97.6)	80.7 (68.1 to 90.0)	85.0 (73.4 to 92.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Good or Moderate EULAR Response at Week 52

End point title	Percentage of Participants Achieving Good or Moderate EULAR Response at Week 52

End point description:

A EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS-28 score. A Good Response is defined as an improvement (decrease) in the DAS28 of more than 1.2 compared with Baseline and attainment of a DAS28 score less than or equal to 3.2. A Moderate Response is defined as either: • an improvement (decrease) in the DAS28 of greater than 0.6 and less than or equal to 1.2 and attainment of a DAS28 score of less than or equal to 5.1 or, • an improvement (decrease) in the DAS28 of more than 1.2 and attainment of a DAS28 score of greater than 3.2. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	62	125	117
Units: percentage of participants				
number (not applicable)	70.0	64.5	68.0	67.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an ACR 50 Response at Week 52

End point title	Percentage of Participants with an ACR 50 Response at Week 52

End point description:

Percentage of participants with an American College of Rheumatology 50% (ACR50) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 50% improvement in 78 tender joint count; • ≥ 50% improvement in 76 swollen joint count; and • ≥ 50% improvement in at least 3 of the 5 following parameters: ◦ Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); ◦ Patient's global assessment of disease activity (measured on a 100 mm VAS); ◦ Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦ Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); ◦C-Reactive Protein. Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	59	62	120	118
Units: percentage of participants				
number (confidence interval 95%)	30.5 (19.2 to 43.9)	27.4 (16.9 to 40.2)	26.7 (19.0 to 35.5)	18.6 (12.1 to 26.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an ACR 70 Response at Week 52

End point title	Percentage of Participants with an ACR 70 Response at Week 52

End point description:

Percentage of participants with an American College of Rheumatology 70% (ACR70) response. A participant was a responder if the following 3 criteria for improvement from Baseline were met: • ≥ 70% improvement in 78 tender joint count; • ≥ 70% improvement in 76 swollen joint count; and • ≥ 70% improvement in at least 3 of the 5 following parameters: ◦ Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); ◦ Patient's global assessment of disease activity (measured on a 100 mm VAS); ◦ Physician's global assessment of disease activity (measured on a 100 mm VAS); ◦ Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index (HAQ-DI)); ◦ C-Reactive Protein. Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	59	63	123	118
Units: percentage of participants				
number (confidence interval 95%)	16.9 (8.4 to 29.0)	14.3 (6.7 to 25.4)	9.8 (5.1 to 16.4)	6.8 (3.0 to 12.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a MASES Score of Zero at Week 52

End point title	Percentage of Participants Achieving a MASES Score of Zero at Week 52

End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improves to 0 after 24 weeks. The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Archilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Two-sided 95% confidence interval is based on the Clopper-Pearson method. Apremilast Subjects as Randomized/Re-randomized Population; subjects with a baseline value > 0 and who had sufficient data for a definitive response at Week 52 are included.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremi last 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	39	80	78
Units: percentage of participants				
number (confidence interval 95%)	42.5 (27.0 to 59.1)	41.0 (25.6 to 57.9)	40.0 (29.2 to 51.6)	37.2 (26.5 to 48.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Dactylitis Score of Zero at Week 52

End point title	Percentage of Participants Achieving a Dactylitis Score of Zero at Week 52

End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improves to zero after 52 weeks. Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present. Two-sided 95% confidence interval is based on the Clopper-Pearson method. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; Participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) and who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo /Apremilast 20 mg	Placebo/Apremi last 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	27	57	60
Units: percentage of participants				
number (confidence interval 95%)	78.3 (56.3 to 92.5)	77.8 (57.7 to 91.4)	57.9 (44.1 to 70.9)	65.0 (51.6 to 76.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events During the Placebo-Controlled Phase

End point title	Number of Participants with Treatment Emergent Adverse Events During the Placebo-Controlled Phase

End point description:

A Treatment Emergent Adverse Event (TEAE) is an AE with a start date on or after the date of the first

dose of Investigational Product (IP). The severity of each adverse event (AE) and serious AE (SAE) was assessed by the investigator and graded based on a scale from Mild to Severe AEs. A serious adverse event (SAE) is any AE which: • Resulted in death • Was life-threatening • Required inpatient hospitalization or prolongation of existing hospitalization • Resulted in persistent or significant disability/incapacity • Was a congenital anomaly/birth defect • Constituted an important medical event; Safety population included all participants who were randomized and received at least one dose of IP.

End point type	Secondary

End point timeframe:

Week 0 to Week 16 for placebo participants who entered EE at Week 16 and up to Week 24 for all other participants (placebo participants who remained on placebo through week 24 and participants randomized to the APR 20 mg BID or APR 30 mg BID)

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	162	
Units: Participants				
Any TEAE|	72	106	96	
Any Drug-Related TEAE|	28	53	57	
Any Severe TEAE|	5	3	11	
Any Serious TEAE (SAE)|	3	6	4	
Any Drug-Related SAE|	0	3	1	
Any TEAE Leading to Drug Interruption|	11	16	31	
Any TEAE Leading to Drug Withdrawal|	3	5	12	
Any TEAE Leading to Death|	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with TEAEs During the Apremilast-Exposure Period

End point title	Number of Participants with TEAEs During the Apremilast-Exposure Period

End point description:

A Treatment Emergent Adverse Event (TEAE) is an AE with a start date on or after the date of the first dose of Investigational Product (IP). The severity of each adverse event (AE) and serious AE (SAE) was assessed by the investigator and graded based on a scale from Mild to Severe AEs. A serious adverse event (SAE) is any AE which: • Resulted in death • Was life-threatening • Required inpatient hospitalization or prolongation of existing hospitalization • Resulted in persistent or significant disability/incapacity • Was a congenital anomaly/birth defect • Constituted an important medical event; apremilast subjects as treated who received at least 1 dose of apremilast at any time during the study.

End point type	Secondary

End point timeframe:

Week 0-260; overall median duration of exposure for APR 20 mg and 30 mg was 198 weeks

End point values	Apremilast 20 mg (Pre-switch)	Apremilast 20 mg/30 mg (Post-switch)	Apremilast 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	113	234	
Units: participants				
Any TEAE|	202	53	207	
Any Drug-related TEAE|	102	5	100	
Any Severe TEAE|	35	2	37	
Any Serious TEAE|	41	5	41	
Any Serious Drug-related TEAE|	6	1	6	
Any TEAE Leading to Drug Interruption|	47	4	65	
Any TEAE Leading to Drug Withdrawal|	24	3	30	
Any TEAE Leading to Death|	0	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

AEs are reported for the placebo-controlled phase from Week 0 - Week 16 for subjects who entered EE at Week 16 and up to Week 24 for all other subjects. AEs are reported for the apremilast exposure period from Week 0 to Week 260.

Adverse event reporting additional description:

Overall median exposure to apremilast was 198 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	V14.0

Reporting groups

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

Reporting group description:

Participants received placebo tablets twice daily during the placebo-controlled phase. Includes data through Week 16 for participants who escaped early, and through Week 24 for all other participants.

Reporting group title	Weeks 0-24: Apremilast 20 mg (Placebo-Controlled Phase)

Reporting group description:

Participants received 20 mg apremilast tablets PO BID during the 24-week placebo-controlled phase.

Reporting group title	Weeks 0-24: Apremilast 30 mg (Placebo-Controlled Phase)

Reporting group description:

Participants received 30 mg apremilast tablets PO BID during the 24-week placebo-controlled phase.

Reporting group title	Apremilast Exposure Period Up to 5 Years: Apremilast 20 mg

Reporting group description:

Participants who received apremilast 20 mg twice daily regardless of when the apremilast exposure started (at Week 0, 16 or 24). Only TEAEs that occurred during apremilast 20 mg BID treatment (before the switch to 30 mg apremilast) were included.

Reporting group title	Apremilast Exposure Up to 5 Years: Apremilast 20/30 mg

Reporting group description:

Subjects who switched from apremilast 20 mg twice daily to apremilast 30 mg twice daily. Only the TEAEs that occurred during apremilast 30 mg twice daily were included.

Reporting group title	Apremilst Exposure up to 5 Years: Apremilast 30 mg

Reporting group description:

Participants who received apremilast 30 mg twice daily throughout the study regardless of when the apremilast-exposure started (at Weeks 0, 16, or 24).

Serious adverse events	Weeks 0-24: Placebo (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 20 mg (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 30 mg (Placebo-Controlled Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 159 (1.89%)	6 / 163 (3.68%)	4 / 162 (2.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign renal neoplasm			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage 0			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-cell lymphoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial thrombosis limb			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian artery stenosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (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
Pelvic floor muscle weakness			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizoaffective disorder			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Contusion			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation of vertebra			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 159 (0.63%)	0 / 163 (0.00%)	0 / 162 (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
Tendon injury			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Hydrocele			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (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
Palpitations			

subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain stem stroke			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery disease			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	1 / 159 (0.63%)	0 / 163 (0.00%)	0 / 162 (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
Headache			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (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
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric volvulus			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichen planus			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired claw toe			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bunion			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 159 (0.63%)	0 / 163 (0.00%)	0 / 162 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroborreliosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin candida			

subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Apremilast Exposure Period Up to 5 Years: Apremilast 20 mg	Apremilast Exposure Up to 5 Years: Apremilast 20/30 mg	Apremilst Exposure up to 5 Years: Apremilast 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 234 (17.52%)	5 / 113 (4.42%)	41 / 234 (17.52%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign renal neoplasm			

subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Breast cancer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Breast cancer metastatic			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage 0			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Prostate cancer			
subjects affected / exposed	1 / 234 (0.43%)	1 / 113 (0.88%)	0 / 234 (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
Prostatic adenoma			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			

subjects affected / exposed	0 / 234 (0.00%)	1 / 113 (0.88%)	0 / 234 (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 cell carcinoma			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
T-cell lymphoma			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Tonsil cancer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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			
Aortic aneurysm			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Arterial thrombosis limb			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Peripheral vascular disorder			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Subclavian artery stenosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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			
Pyrexia			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Pelvic floor muscle weakness			

subjects affected / exposed	0 / 234 (0.00%)	1 / 113 (0.88%)	0 / 234 (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
Uterine haemorrhage			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Uterine prolapse			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Vaginal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Pulmonary fibrosis			

subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Depression			
subjects affected / exposed	3 / 234 (1.28%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizoaffective disorder			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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			
Ankle fracture			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Dislocation of vertebra			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Foreign body			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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

Graft haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Limb injury			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain stem stroke			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery disease			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diabetic neuropathy			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Tension headache			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric volvulus			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Hernial eventration			

subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Pancreatitis acute			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Lichen planus			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Psoriasis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure acute			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired claw toe			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bunion			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	3 / 234 (1.28%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Osteoarthritis			
subjects affected / exposed	2 / 234 (0.85%)	1 / 113 (0.88%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	0 / 234 (0.00%)	1 / 113 (0.88%)	0 / 234 (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
Arthritis infective			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 113 (0.88%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Lobar pneumonia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Neuroborreliosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Oral candidiasis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Peritoneal abscess			

subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Pneumonia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Scrotal abscess			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 234 (0.00%)	0 / 113 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin candida			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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
Urinary tract infection bacterial			
subjects affected / exposed	1 / 234 (0.43%)	0 / 113 (0.00%)	0 / 234 (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			
Hyponatraemia			
subjects affected / exposed	2 / 234 (0.85%)	0 / 113 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Weeks 0-24: Placebo (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 20 mg (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 30 mg (Placebo-Controlled Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 159 (23.90%)	73 / 163 (44.79%)	82 / 162 (50.62%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 159 (4.40%)	4 / 163 (2.45%)	5 / 162 (3.09%)
occurrences (all)	7	4	5
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 159 (4.40%)	9 / 163 (5.52%)	18 / 162 (11.11%)
occurrences (all)	8	11	18
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 159 (0.63%)	4 / 163 (2.45%)	2 / 162 (1.23%)
occurrences (all)	1	6	2
Abdominal pain upper			
subjects affected / exposed	0 / 159 (0.00%)	4 / 163 (2.45%)	5 / 162 (3.09%)
occurrences (all)	0	5	5
Diarrhoea			
subjects affected / exposed	8 / 159 (5.03%)	18 / 163 (11.04%)	25 / 162 (15.43%)
occurrences (all)	9	24	30
Dyspepsia			
subjects affected / exposed	1 / 159 (0.63%)	4 / 163 (2.45%)	5 / 162 (3.09%)
occurrences (all)	1	4	5
Nausea			
subjects affected / exposed	3 / 159 (1.89%)	15 / 163 (9.20%)	26 / 162 (16.05%)
occurrences (all)	3	18	28
Vomiting			
subjects affected / exposed	2 / 159 (1.26%)	5 / 163 (3.07%)	6 / 162 (3.70%)
occurrences (all)	2	6	7
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 159 (0.00%)	4 / 163 (2.45%)	3 / 162 (1.85%)
occurrences (all)	0	4	3
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 159 (1.26%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	2	1	0
Insomnia			
subjects affected / exposed	0 / 159 (0.00%)	3 / 163 (1.84%)	1 / 162 (0.62%)
occurrences (all)	0	3	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 159 (0.00%)	5 / 163 (3.07%)	3 / 162 (1.85%)
occurrences (all)	0	5	5
Osteoarthritis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 159 (0.00%)	5 / 163 (3.07%)	6 / 162 (3.70%)
occurrences (all)	0	5	6
Influenza			
subjects affected / exposed	0 / 159 (0.00%)	4 / 163 (2.45%)	3 / 162 (1.85%)
occurrences (all)	0	6	3
Nasopharyngitis			
subjects affected / exposed	6 / 159 (3.77%)	9 / 163 (5.52%)	9 / 162 (5.56%)
occurrences (all)	6	9	10
Pharyngitis			
subjects affected / exposed	2 / 159 (1.26%)	1 / 163 (0.61%)	2 / 162 (1.23%)
occurrences (all)	3	1	2
Rhinitis			
subjects affected / exposed	1 / 159 (0.63%)	1 / 163 (0.61%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	4 / 159 (2.52%)	4 / 163 (2.45%)	3 / 162 (1.85%)
occurrences (all)	5	4	3
Upper respiratory tract infection			

subjects affected / exposed	6 / 159 (3.77%)	14 / 163 (8.59%)	11 / 162 (6.79%)
occurrences (all)	6	18	11
Urinary tract infection			
subjects affected / exposed	2 / 159 (1.26%)	3 / 163 (1.84%)	1 / 162 (0.62%)
occurrences (all)	2	3	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 159 (0.63%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	Apremilast Exposure Period Up to 5 Years: Apremilast 20 mg	Apremilast Exposure Up to 5 Years: Apremilast 20/30 mg	Apremilst Exposure up to 5 Years: Apremilast 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 234 (65.81%)	19 / 113 (16.81%)	166 / 234 (70.94%)
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 234 (8.97%)	4 / 113 (3.54%)	22 / 234 (9.40%)
occurrences (all)	21	5	26
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 234 (9.83%)	0 / 113 (0.00%)	29 / 234 (12.39%)
occurrences (all)	28	0	31
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 234 (5.98%)	0 / 113 (0.00%)	9 / 234 (3.85%)
occurrences (all)	17	0	12
Abdominal pain upper			
subjects affected / exposed	11 / 234 (4.70%)	1 / 113 (0.88%)	13 / 234 (5.56%)
occurrences (all)	17	1	13
Diarrhoea			
subjects affected / exposed	33 / 234 (14.10%)	0 / 113 (0.00%)	40 / 234 (17.09%)
occurrences (all)	47	0	55
Dyspepsia			
subjects affected / exposed	12 / 234 (5.13%)	0 / 113 (0.00%)	12 / 234 (5.13%)
occurrences (all)	13	0	13
Nausea			

subjects affected / exposed	25 / 234 (10.68%)	1 / 113 (0.88%)	37 / 234 (15.81%)
occurrences (all)	31	1	40
Vomiting			
subjects affected / exposed	10 / 234 (4.27%)	1 / 113 (0.88%)	12 / 234 (5.13%)
occurrences (all)	11	1	17
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 234 (5.13%)	0 / 113 (0.00%)	15 / 234 (6.41%)
occurrences (all)	15	0	19
Psychiatric disorders			
Depression			
subjects affected / exposed	13 / 234 (5.56%)	0 / 113 (0.00%)	7 / 234 (2.99%)
occurrences (all)	14	0	10
Insomnia			
subjects affected / exposed	14 / 234 (5.98%)	0 / 113 (0.00%)	12 / 234 (5.13%)
occurrences (all)	14	0	15
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	22 / 234 (9.40%)	0 / 113 (0.00%)	14 / 234 (5.98%)
occurrences (all)	25	0	19
Osteoarthritis			
subjects affected / exposed	11 / 234 (4.70%)	2 / 113 (1.77%)	12 / 234 (5.13%)
occurrences (all)	12	2	13
Infections and infestations			
Bronchitis			
subjects affected / exposed	19 / 234 (8.12%)	1 / 113 (0.88%)	30 / 234 (12.82%)
occurrences (all)	34	1	40
Influenza			
subjects affected / exposed	13 / 234 (5.56%)	0 / 113 (0.00%)	10 / 234 (4.27%)
occurrences (all)	20	0	12
Nasopharyngitis			
subjects affected / exposed	28 / 234 (11.97%)	4 / 113 (3.54%)	30 / 234 (12.82%)
occurrences (all)	40	4	49
Pharyngitis			
subjects affected / exposed	8 / 234 (3.42%)	1 / 113 (0.88%)	15 / 234 (6.41%)
occurrences (all)	10	1	19

Rhinitis			
subjects affected / exposed	5 / 234 (2.14%)	0 / 113 (0.00%)	13 / 234 (5.56%)
occurrences (all)	8	0	14
Sinusitis			
subjects affected / exposed	17 / 234 (7.26%)	1 / 113 (0.88%)	15 / 234 (6.41%)
occurrences (all)	26	1	18
Upper respiratory tract infection			
subjects affected / exposed	42 / 234 (17.95%)	4 / 113 (3.54%)	37 / 234 (15.81%)
occurrences (all)	73	7	69
Urinary tract infection			
subjects affected / exposed	18 / 234 (7.69%)	4 / 113 (3.54%)	13 / 234 (5.56%)
occurrences (all)	24	4	17
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	14 / 234 (5.98%)	0 / 113 (0.00%)	7 / 234 (2.99%)
occurrences (all)	14	0	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2011	1. Modification of protocol language for clarification. 2. Clarification of the language around contraception methods to ensure precise description of acceptable methods of contraception given the global nature of Celgene's trials. In addition, a statement was added into the protocol to ensure that appropriate education regarding contraception methods was provided by the investigator to the subject. 3. Modification to protocol deleting annual chest radiographs allowing local treatment guidelines to dictate when chest radiographs were performed. 4. BSA involved by psoriasis added as study assessment. 5. Alignment of exclusion criteria related to past malignancies across the entire APR Phase 3 program that gave investigators responsibility for determining subject eligibility for previously successfully treated local lesions. 6. Modification of Reasons for Discontinuation to align with what was displayed in the Inform database.
10 June 2011	1. Provided correction regarding the Celgene Therapeutic Area Head of the study. 2. Addition of a serum pregnancy test at baseline for FCBP. 3. A clarification in Section 6.2, Contraception Education, which directed the investigator to Section 7.2 of the protocol where the specific details regarding acceptable contraception for this study were found. 4. A clarification in Section 6.6.4, Clinical Laboratory Evaluations, to indicate that a microscopic evaluation was to be performed on all urine samples. 5. Modification to Inclusion Criterion Number 14 – The Female Birth Control Inclusion Criterion was updated to clearly define single or multiple forms of contraception that were acceptable for this study. 6. Addition of a footnote to Inclusion Criterion Number 14 – The Female Birth Control Inclusion Criteria, which clarified that the female subject's chosen form of contraception must be fully effective by the time the female subject received the first dose of study medication at randomization. 7. Modification to Inclusion Criterion Number 13 – Male Birth Control Inclusion Criteria, which clarified that male subjects must use a "male" latex or non-latex condom. 8. Descriptive text on how to record onset and end dates of SAEs on the SAE Report Form was deleted because it was no longer applicable.
20 April 2012	1. Provided updates to the contact information for the Medical Monitor of the study. 2. Modification of Section 4.1 Study Design, Section 8.2 Treatment Administration and Schedule, and Section 10.1 Overview regarding site and subject blinding until completion of the 52 Week double-blind phase. 3. Revision of Section 4.1 regarding the replacement of the SRP with an independent external DMC. 4. Modification of Section 4.2 Study Design Rationale, Section 9.1 Permitted Concomitant Medications and Procedures, and Section 9.2 Prohibited Concomitant Medications and Procedures to allow the use of topical therapy and/or phototherapy after the Week 52 study visit for worsening skin psoriasis. 5. Addition of a footnote to the Adverse Events row in Table of Events, Section 5, (Tables 1 and 2) which reminded investigators to perform vasculitis assessments and/or psychiatric evaluations as appropriate, when AEs were reported. 6. A revision of the Contraception Education in Section 6.2 and movement of footnote from Section 7.2 to Section 6.2. 7. Addition of Section 6.6.3.1 Vasculitis Assessment providing guidance to investigators. 8. Addition of Section 6.6.3.2 Psychiatric Evaluation to provide guidance to investigators for the management of subjects identified as having thoughts of suicide, attempted suicide, or having a major psychiatric illness. 9. Addition of Section 6.6.3.3 Risk Benefit for Long-term Active Treatment providing guidance to investigators regarding radiographs of symptomatic joints. 10. A change to the open-label IP packaging is described in Sections 6.9.1 and 8.4. 11. A note was added to Section 7.2, Inclusion Criterion 14, to refer investigators to Section 6.2, Contraception Education. 12. AE tables will summarize TEAEs only. 13. The term "CRF" (case report form) was changed to "eCRF" globally throughout the document to reflect that data is captured in this study in electronic case report form pages (eCRF).

03 July 2012	1. The assessment of the primary efficacy endpoint (ACR 20) was changed to Week 16 instead of Week 24. 2. Assessments of enthesitis and dactylitis (in subjects who present with these manifestations of PsA at baseline) were elevated to be secondary rather than exploratory outcome measures. 3. The secondary endpoints were to be assessed at Week 16, in addition to Weeks 24 and 52. 4. The order of secondary endpoints at Weeks 16, 24 and 52 was modified to coincide with the planned sequence of statistical testing. 5. The modified PsARC and EULAR response were added as secondary efficacy endpoints. 6. The ACR-N was added as an exploratory endpoint. 7. The health-related quality of life endpoints were to be assessed at Week 16, in addition to Weeks 24 and 52. 8. Modification of Section 9.1 Permitted Concomitant Medications to allow use of systemic corticosteroids and DMARDs after the Week 52 study visit for worsening arthritic symptoms of PsA 9. The statistical approaches for analysis of secondary endpoints were updated. 10. The statistical approaches for subgroup analyses were updated. 11. Citations were included to provide references for the modified PsARC and EULAR response that were added as secondary efficacy outcome measures in this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27422893