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	2010-018385-23
Trial protocol	DE HU AT FR GB ES
Global end of trial date	27 October 2016

Results information

Result version number	v1 (current)
This version publication date	12 November 2017
First version publication date	12 November 2017

Trial information

Trial identification

Sponsor protocol code	CC-10004-PSA-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01172938
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Nikolay Delev, Senior Director, Clinical Research and Development, M.D., 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	16 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of 2 doses of apremilast (20 mg or 30 mg orally twice per day [BID]), compared with placebo, on the signs and symptoms of psoriatic arthritis (PsA) after 16 weeks' administration.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason
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	Australia: 21
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Canada: 88
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	New Zealand: 20
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	South Africa: 74
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 135
Worldwide total number of subjects	504
EEA total number of subjects	122

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)	452
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was a multicenter study with 83 study sites from the US, Canada, Europe, Russia, Australia, New Zealand and South Africa.

Pre-assignment

Screening details:

The study population was restricted to male and female subjects ≥ 18 years of age with moderate to severe Psoriatic Arthritis (PsA). Participants must have had a diagnosis of PsA by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, including peripheral joint involvement.

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	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	Placebo

Arm description:

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

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

Dosage and administration details:

Identically matched placebo tablets BID during the placebo controlled phase.

Arm title	Apremilast 20 mg

Arm description:

Subjects initially randomized to receive 20 mg apremilast tablets twice daily in the 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 BID during the placebo controlled phase.

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the 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 BID during the placebo controlled phase.

Number of subjects in period 1	Placebo	Apremilast 20 mg	Apremilast 30 mg
Started	168	168	168
Received Treatment	168	168	168
Completed Week (Wk) 16	158	158	154
Early Escape (EE) at Week 16	107 [1]	78 [2]	58 [3]
Completed	150	146	148
Not completed	18	22	20
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	2	5	3
Adverse event, non-fatal	11	8	10
Not specified	-	2	1
Non-compliance with study drug	-	1	2
Lack of efficacy	4	5	4
Protocol deviation	1	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will 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: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will 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: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

Period 2

Period 2 title	Active Treatment Phase (Weeks 25-52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase continued to receive 20 mg apremilast tablets BID in the active treatment.

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 PO BID

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 mg apremilast tablets BIDin 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 BID

Arm title	Placebo / Apremilast 20 mg EE

Arm description:

Subjects initially randomized to receive placebo twice daily who were re-randomized due to early escape (EE) at Week 16 continued to receive 20 mg apremilast 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 BID

Arm title	Placebo / Apremilast 20 mg XO

Arm description:

Subjects initially randomized to receive placebo twice daily who were re-randomized at Week 24 (XO)

continued to receive 20 mg apremilast tablets BID 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 BID

Arm title	Placebo / Apremilast 30 mg EE

Arm description:

Subjects initially randomized to receive placebo twice daily who were re-randomized due to early escape (EE) at Week 16 continued to receive 30 mg apremilast tablets BID 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 BID

Arm title	Placebo / Apremilast 30 mg XO

Arm description:

Subjects initially randomized to receive placebo twice daily who were re-randomized at Week 24 continued to receive 30 mg apremilast tablets BID 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 BID

Number of subjects in period 2[4]	Apremilast 20 mg	Apremilast 30 mg	Placebo / Apremilast 20 mg EE
Started	136	145	51
Completed	124	130	44
Not completed	12	15	7
Consent withdrawn by subject	5	1	2
Adverse event, non-fatal	2	5	1
Not specified	-	-	-
Non-compliance with study drug	-	1	-
Lost to follow-up	1	1	1
Lack of efficacy	4	7	3

Number of subjects in period 2[4]	Placebo / Apremilast 20 mg XO	Placebo / Apremilast 30 mg EE	Placebo / Apremilast 30 mg XO
Started	23	49	24
Completed	19	34	22
Not completed	4	15	2
Consent withdrawn by subject	2	9	1
Adverse event, non-fatal	1	2	-
Not specified	-	1	1
Non-compliance with study drug	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	1	3	-

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: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

Period 3

Period 3 title	Active-Treatment Phase (Weeks 52-104)
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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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 PO BID

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 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 30 mg tablets PO BID

Arm title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and 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:

Initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg BID for up to 4.5 years in the active treatment / long-term safety phase.

Arm title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and 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:

Initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and continued receiving apremilast 20 mg BID for up to 4.5 years in the active treatment / long-term safety phase.

Number of subjects in period 3[5]	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)
Started	118	121	61
Completed	95	100	46
Not completed	23	21	15
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	10	8	5
Adverse event, non-fatal	2	1	3
Miscellaneous	2	-	-

Non-compliance with study drug	-	2	-
Lost to follow-up	1	1	3
Missing	1	-	-
Lack of efficacy	7	8	4

Number of subjects in period 3[5]	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)
Started	49
Completed	45
Not completed	4
Adverse event, serious fatal	-
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Miscellaneous	1
Non-compliance with study drug	-
Lost to follow-up	-
Missing	-
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: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

Period 4

Period 4 title	Active-Treatment Phase Weeks (104-156)
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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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 PO BID

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 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 30 mg tablets PO BID

Arm title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and continued to receive apremilast 20 mg BID in the active treatment / long-term safety phase. After 30 mg apremilast BID was identified as the optimal dose, all subjects originally 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 PO BID

Arm title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and 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 PO BID

Number of subjects in period 4	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)
Started	95	100	46
Completed	84	93	41
Not completed	11	7	5
Adverse event, serious fatal	-	-	1

Consent withdrawn by subject	6	3	2
Adverse event, non-fatal	-	-	-
Miscellaneious	-	2	-
Lost to follow-up	1	-	-
Lack of efficacy	4	2	2

Number of subjects in period 4	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)
Started	45
Completed	41
Not completed	4
Adverse event, serious fatal	-
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Miscellaneious	-
Lost to follow-up	-
Lack of efficacy	2

Period 5

Period 5 title	Active-Treatment Phase (Weeks 156-208)
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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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 PO BID

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 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 30 mg tablets PO BID

Arm title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and continued to receive apremilast 20 mg BID in the active treatment / long-term safety phase. After 30 mg apremilast BID was identified as the optimal dose, all subjects originally 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 PO BID

Arm title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued to receive 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 PO BID

Number of subjects in period 5	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)
Started	84	93	41
Completed	75	88	32
Not completed	9	5	9
Consent withdrawn by subject	4	2	2
Adverse event, non-fatal	4	1	3
Miscellaneous	-	-	1
Lost to follow-up	-	1	-

Lack of efficacy	1	1	3

Number of subjects in period 5	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)
Started	41
Completed	34
Not completed	7
Consent withdrawn by subject	4
Adverse event, non-fatal	-
Miscellaneous	-
Lost to follow-up	1
Lack of efficacy	2

Period 6

Period 6 title	Active-Treatment Phase (Weeks 208-260)
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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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 subjects originally 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 PO BID

Arm title	Apremilast 30 mg

Arm description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 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 30 mg tablets PO BID

Arm title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast at Week 16 or Week 24 and continued to receive apremilast 20 mg BID in the active treatment / long-term safety phase. After 30 mg apremilast BID was identified as the optimal dose, all subjects originally 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 PO BID

Arm title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Arm description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and were re-randomized to apremilast 30 mg tablets BID at Week 16 or Week 24 and continued to receive 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 PO BID

Number of subjects in period 6	Apremilast 20 mg	Apremilast 30 mg	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)
Started	75	88	32
Switched from 20 mg to 30 mg BID	62 [6]	0 [7]	25 [8]
Completed	72	80	29
Not completed	3	8	3
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	2	3	1
Adverse event, non-fatal	-	1	1
Non-compliance with study drug	1	-	1
Lost to follow-up	-	1	-

Lack of efficacy	-	2	-
Protocol deviation	-	-	-

Number of subjects in period 6	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)
Started	34
Switched from 20 mg to 30 mg BID	0 [9]
Completed	32
Not completed	2
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Non-compliance with study drug	-
Lost to follow-up	-
Lack of efficacy	-
Protocol deviation	1

Notes:

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects starting the subsequent period will be less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period will enter the subsequent period.

Baseline characteristics

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

Reporting group values	Placebo	Apremilast 20 mg	Apremilast 30 mg
Number of subjects	168	168	168
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)	149	157	146
From 65-84 years	19	11	22
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.1	48.7	51.4
standard deviation	± 12.13	± 10.99	± 11.72
Gender, Male/Female Units: Subjects			
Female	80	83	92
Male	88	85	76
Study Specific Characteristic | Duration of psoriatic arthritis Units: years			
arithmetic mean	7.31	7.18	8.09
standard deviation	± 7.118	± 6.842	± 8.092

Reporting group values	Total		
Number of subjects	504		
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)	452		
From 65-84 years	52		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	255		
Male	249		
Study Specific Characteristic | Duration of psoriatic arthritis			
Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

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

Reporting group title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and 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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 mg apremilast tablets BID in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

Subjects initially randomized to placebo tablets BID during the placebo controlled phase and 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:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 mg apremilast tablets BID in the active treatment / long-term safety phase

Reporting group title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

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

Reporting group title	Apremilast 20 mg

Reporting group description:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and 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 subjects originally receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose

Reporting group title	Apremilast 30 mg

Reporting group description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID) in the placebo-controlled phase and continued to receive 30 mg apremilast tablets BID in the active treatment / long-term safety phase

Reporting group title	Placebo/Apremilast 20 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Active-Treatment/Long-Term Safety)

Reporting group description:

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

Subject analysis set title	Placebo / Apremilast 20 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received placebo twice daily up to Week 16 or Week 24 and were then re-randomized to receive 20 mg apremilast twice daily.

Subject analysis set title	Placebo / Apremilast 30 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received placebo twice daily up to Week 16 or Week 24 and were then re-randomized to receive 30 mg apremilast twice daily.

Subject analysis set title	Apremilast 20 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects initially randomized to 20 mg apremilast tablets twice daily (BID).

Subject analysis set title	Apremilast 30 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects initially randomized to 30 mg apremilast tablets twice daily (BID).

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

Subject analysis set description:

Subjects randomized or re-randomized to apremilast 20 mg BID ; only the 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 BID (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 counted.

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

Subject analysis set description:

Participants who were treated with apremilast 30 mg BID throughout the study 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 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. Full analysis set (FAS) consisting of all participants randomized as specified in the protocol. Participants who withdrew 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	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	168	168	168	
Units: percentage of participants				
number (not applicable)	19.0	30.4	38.1	

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	336
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.7
upper limit	28.3

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	336
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0166 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	20.4

Notes:

[3] - 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.

[4] - 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. Full analysis set; participants with a baseline value and at least 1 postbaseline 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	165	163	159	
Units: units on a scale				
least squares mean (standard error)	-0.086 (± 0.0360)	-0.198 (± 0.0364)	-0.244 (± 0.0364)	

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	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.258
upper limit	-0.06

Notes:

[5] - Based on an 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	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0252 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.113

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.211
upper limit	-0.014

Notes:

[6] - 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 at Week 24. 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; 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	168	168	168	
Units: percentage of participants				
number (not applicable)	13.1	25.6	35.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	22.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	13.4
upper limit	30.9

Notes:

[7] - 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.
[8] - 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:

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.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0038 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	20.7

Notes:

[9] - 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.
[10] - 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. 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	165	163	161	
Units: units on a scale				
least squares mean (standard error)	-0.076 (± 0.0369)	-0.211 (± 0.0373)	-0.258 (± 0.0371)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.283
upper limit	-0.08

Notes:

[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

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.236
upper limit	-0.034

Notes:

[12] - 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 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	163	163	159	
Units: units on a scale				
least squares mean (standard error)	1.81 (± 0.621)	3.50 (± 0.625)	4.23 (± 0.625)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	4.13

Notes:

[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.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0504 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.4

Notes:

[14] - 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, 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 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168	168	168	
Units: percentage of participants				
number (not applicable)	29.8	38.7	46.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0017 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	26.8

Notes:

[15] - 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.
[16] - 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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	18.9

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	165	163	159	
Units: mm				
least squares mean (standard error)	-5.7 (± 1.83)	-11.5 (± 1.85)	-13.5 (± 1.85)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	-2.8

Notes:

[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.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-5.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-0.7

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	95	100	108	
Units: units on a scale				
least squares mean (standard error)	-0.9 (± 0.30)	-1.4 (± 0.29)	-1.3 (± 0.28)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.3

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 severity 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	56	66	
Units: units on a scale				
least squares mean (standard error)	-1.4 (± 0.28)	-1.9 (± 0.31)	-1.7 (± 0.28)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.3

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 to 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	158	160	158	
Units: units on a scale				
least squares mean (standard error)	-3.84 (± 0.929)	-8.24 (± 0.926)	-8.72 (± 0.923)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-4.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.41
upper limit	-2.34

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-4.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.92
upper limit	-1.86

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	159	161	154	
Units: units on a scale				
least squares mean (standard error)	-0.26 (± 0.082)	-0.73 (± 0.082)	-0.79 (± 0.083)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.31

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.25

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	162	163	159	
Units: units on a scale				
least squares mean (standard error)	1.55 (± 0.693)	1.68 (± 0.696)	3.88 (± 0.695)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	4.23

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	2.03

Secondary: Change from Baseline in SF-36 Physical Function at Week 24

End point title	Change from Baseline in SF-36 Physical Function 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 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	163	163	161	
Units: units on a scale				
least squares mean (standard error)	1.45 (± 0.671)	3.49 (± 0.675)	5.01 (± 0.671)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	3.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	5.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	3.88

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	168	168	168	
Units: percentage of participants				
number (not applicable)	18.5	31.0	42.9	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	24.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.2
upper limit	34

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	21.5

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 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	165	163	162	
Units: mm				
least squares mean (standard error)	-4.2 (± 1.78)	-11.2 (± 1.79)	-14.7 (± 1.77)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	-10.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-5.7

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-2.2

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 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	96	100	110	
Units: units on a scale				
least squares mean (standard error)	-0.8 (± 0.31)	-1.6 (± 0.30)	-1.6 (± 0.29)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean DIfference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.1

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 severity 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	64	56	66	
Units: units on a scale				
least squares mean (standard error)	-1.3 (± 0.27)	-2.0 (± 0.30)	-1.8 (± 0.27)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.3

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.1

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	158	161	161	
Units: units on a scale				
least squares mean (standard error)	-3.14 (± 0.965)	-7.55 (± 0.958)	-9.52 (± 0.949)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean Difference
Point estimate	-6.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	-3.75

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean Difference
Point estimate	-4.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.03
upper limit	-1.79

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	161	161	159	
Units: units on a scale				
least squares mean (standard error)	-0.20 (± 0.087)	-0.66 (± 0.087)	-0.90 (± 0.087)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.46

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on an analysis of covariance (ANCOVA) model with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.	
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.22

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	163	163	161	
Units: units on a scale				
least squares mean (standard error)	1.12 (± 0.691)	1.52 (± 0.696)	3.33 (± 0.690)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean Difference
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	4.1

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo v Apremilast 20 mg

Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean DIfference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.29

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	98	103	114	
Units: percentage of participants				
number (not applicable)	49.0	56.3	52.6	

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	212
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	16.7

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	201
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	21.1

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 severity 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	68	59	68	
Units: percentage of participants				
number (not applicable)	57.4	66.1	60.3	

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	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	19.3

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	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	24.6

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	168	168	168	
Units: percentage of participants				
number (not applicable)	29.8	46.4	48.8	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	19.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	29.3

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.4
upper limit	26.8

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 subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% from Baseline 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. FAS; subjects with a baseline MASES > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for those who escaped early at subjects 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	98	103	114	
Units: percentage of participants				
number (not applicable)	46.9	58.3	60.5	

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	212
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	26.5

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	201
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	25

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 severity 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	68	59	68	
Units: percentage of participants				
number (not applicable)	60.3	69.5	69.1	

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	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	24.6

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	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	24.2

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	168	168	168	
Units: percentage of participants				
number (not applicable)	16.1	30.4	42.3	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.1
upper limit	35.5

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	23.1

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: ◦ 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, 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	168	168	168	
Units: percentage of participants				
number (not applicable)	6.0	15.5	16.1	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	16.8

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	16

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: ◦ 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, 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	168	168	168	
Units: percentage of participants				
number (not applicable)	1.2	6.0	4.2	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	6.5

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	8.7

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: ◦ 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	168	168	168	
Units: percentage of participants				
number (not applicable)	4.2	14.3	19.0	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.3
upper limit	21.5

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	16.1

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	168	168	168	
Units: percentage of participants				
number (not applicable)	0.6	5.4	10.1	

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	14.2

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	336
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	8.3

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	98	103	114	
Units: percentage of participants				
number (not applicable)	15.3	27.2	22.8	

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	212
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	17.9

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	201
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	23

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 severity 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	68	59	68	
Units: percentage of participants				
number (not applicable)	39.7	42.4	38.2	

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	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	14.8

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	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	19.6

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. FAS; subjects with a baseline MASES > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for subjects who escaped early at Week 16. Subjects 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:

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	98	103	114	
Units: percentage of participants				
number (not applicable)	14.3	31.1	31.6	

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	212
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	28.2

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	201
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	27.9

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 severity 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:

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)	39.7	49.2	45.6	

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	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	22.4

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	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Difference
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	26.2

Secondary: Number of Participants with Adverse Events During the Placebo-Controlled Period

End point title	Number of Participants with Adverse Events During the

	Placebo-Controlled 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). An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Week 0 to Week 16 for placebo participants who entered early escape 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	168	168	168	
Units: participants				
Treatment Emergent Adverse Events	81	101	103	
Drug-related TEAE	32	54	70	
Severe TEAE	6	8	11	
Serious TEAE (SAE)	7	8	9	
Drug-related Serious AE	2	0	3	
TEAE Leading to Drug Interruption	9	10	17	
TEAE Leading to Drug Withdrawal	8	10	12	
TEAE Leading to Death	0	1	0	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

A TEAE is an AE with a start date on or after the date of the first dose of Investigational Product (IP) and no later than 28 days after the last dose of IP. An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Baseline to Week 260; median total exposure to Apremilast was 170 weeks

End point values	Apremilast 20 mg (Pre-switch)	Apremilast 20 mg/30 mg BID (post-switch)	Apremilast 30 mg BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	245	87	245	
Units: participants				
Treatment Emergent Adverse Events (TEAEs)	203	39	213	
Drug-related TEAE	96	5	131	
Severe TEAE	35	1	30	
Serious TEAE (SAE)	41	6	49	
Drug-related SAE	4	1	9	
TEAE leading to drug interruption	47	3	49	
TEAE leading to drug withdrawal	27	0	30	
TEAE leading to death	1	0	2	

Statistical analyses

No statistical analyses for this end point

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:

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. 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	64	60	119	130
Units: Participants				
number (confidence interval 95%)	53.1 (40.2 to 65.7)	50.0 (36.8 to 63.2)	63.0 (53.7 to 71.7)	54.6 (45.7 to 63.4)

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 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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population.

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	64	61	120	132
Units: units on a scale				
arithmetic mean (standard deviation)	-0.27 (± 0.562)	-0.29 (± 0.590)	-0.37 (± 0.479)	-0.32 (± 0.547)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the SF-36 Physical Functioning Domain at Week 52

End point title	Change From Baseline in the SF-36 Physical Functioning Domain 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. 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	64	61	120	130
Units: units on a scale				
arithmetic mean (standard deviation)	4.46 (± 8.8877)	4.62 (± 9.979)	6.98 (± 9.425)	5.69 (± 8.995)

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 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,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; includes those who had sufficient data of response status 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	61	59	120	129
Units: subjects				
number (confidence interval 95%)	73.8 (60.9 to 84.2)	71.2 (57.9 to 82.2)	77.5 (69.0 to 84.6)	73.6 (65.2 to 81.0)

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	64	60	120	131
Units: mm				
arithmetic mean (standard deviation)	-20.2 (± 26.76)	-21.0 (± 25.83)	-17.8 (± 24.50)	-20.3 (± 23.37)

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.

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	36	36	69	89
Units: units on a scale				
arithmetic mean (standard deviation)	-2.2 (± 4.03)	-1.9 (± 3.89)	-2.7 (± 2.41)	-1.9 (± 2.93)

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 severity 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. 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	26	48	49
Units: units on a scale				
arithmetic mean (standard deviation)	-0.8 (± 2.10)	-2.4 (± 3.58)	-2.7 (± 3.79)	-1.8 (± 3.23)

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. 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	61	59	120	129
Units: units on a scale				
arithmetic mean (standard deviation)	-15.00 (± 11.137)	-14.03 (± 14.900)	-15.41 (± 13.039)	-14.54 (± 12.009)

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. 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	64	60	120	129
Units: units on a scale				
arithmetic mean (standard deviation)	-1.47 (± 1.103)	-1.15 (± 1.272)	-1.40 (± 1.125)	-1.31 (± 1.114)

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	63	61	120	128
Units: units on a scale				
arithmetic mean (standard deviation)	4.33 (± 8.183)	4.15 (± 11.712)	4.27 (± 8.488)	3.67 (± 9.078)

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.

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	36	36	69	89
Units: percentage of subjects				
number (confidence interval 95%)	69.4 (51.9 to 83.7)	55.6 (38.1 to 72.1)	84.1 (73.3 to 91.8)	75.3 (65.0 to 83.8)

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 severity 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. 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	26	48	49
Units: percentage of subjects				
number (confidence interval 95%)	65.2 (42.7 to 83.6)	73.1 (52.2 to 88.4)	85.4 (72.2 to 93.9)	77.6 (63.4 to 88.2)

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. 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	64	60	120	129
Units: percentage of subjects				
number (not applicable)	82.8	70.0	75.0	74.4

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. 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	63	61	117	130
Units: percentage of subjects				
number (confidence interval 95%)	25.4 (15.3 to 37.9)	27.9 (17.1 to 40.8)	24.8 (17.3 to 33.6)	24.6 (17.5 to 32.9)

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. 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	62	61	117	130
Units: percentage of subjects				
number (confidence interval 95%)	4.8 (1.0 to 13.5)	14.8 (7.0 to 26.2)	15.4 (9.4 to 23.2)	13.8 (8.4 to 21.0)

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 (AAR) Population; only those participants with a baseline value > 0 (i.e., pre-existing enthesopathy) 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 / 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	36	36	69	89
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (18.6 to 51.0)	27.8 (14.2 to 45.2)	50.7 (38.4 to 63.0)	38.2 (28.1 to 49.1)

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 severity 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. 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 / 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	26	48	49
Units: percentage of subjects				
number (confidence interval 95%)	52.2 (30.6 to 73.2)	53.8 (33.4 to 73.4)	68.8 (53.7 to 81.3)	68.3 (48.3 to 76.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events During the Apremilast-Exposure Period

End point title	Number of Subjects with Adverse Events During the Apremilast-Exposure Period

End point description:

A TEAE is an AE with a start date on or after the date of the first dose of Investigational Product (IP) and no later than 28 days after the last dose of IP. An AE is any noxious, unintended, or untoward medical occurrence, that may appear or worsen in a participant during the course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Baseline to Week 260; median total exposure to Apremilast was 170 weeks

End point values	Apremilast 20 mg (Pre-switch)	Apremilast 20 mg/30 mg BID (post-switch)	Apremilast 30 mg BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	245	87	245	
Units: subjects				
Treatment Emergent Adverse Events (TEAEs)	203	39	213	
Drug-related TEAE	96	5	131	
Severe TEAE	35	1	30	
Serious TEAE (SAE)	41	6	49	
Drug-related SAE	4	1	9	
TEAE Leading to Drug Interruption	47	3	49	
TEAE Leading to Drug Withdrawal	27	0	30	
TEAE Leading to Death	1	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo-controlled Phase: Week 0 to Week 16 for placebo subjects who entered early escape at Week 16 and up to Week 24 for all other subjects. Apremilast-exposure Phase: Baseline to Week 260; median total exposure to Apremilast was 170 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	V14.0

Reporting groups

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

Reporting group description:

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

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

Reporting group description:

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

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

Reporting group description:

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

Reporting group title	Apremilast Exposure up to 5 Years: Apremilast 20 mg

Reporting group description:

Subjects randomized or re-randomized to apremilast 20 mg BID. Only the 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 BID

Reporting group description:

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

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

Reporting group description:

Subjects who were treated with apremilast 30 mg BID throughout the study regardless of when their apremilast-exposure started (at Weeks 0, 16, or 24).

Serious adverse events	Week 0-24: Placebo (Placebo-Controlled Phase)	Week 0-24: Apremilast 20 mg (Placebo- Controlled Phase)	Week 0-24: Apremilast 30 mg (Placebo- Controlled Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 168 (4.17%)	8 / 168 (4.76%)	9 / 168 (5.36%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Metastases to lymph nodes			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Morton's neuroma			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Neuroendocrine tumour			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
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 crisis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Hypotension			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Varicose vein			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Multi-organ failure			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Pyrexia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Adnexa uteri cyst			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (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
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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

Endometriosis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Ovarian cyst ruptured			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Asthma			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Bronchiectasis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Haemoptysis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Pleural effusion			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 embolism			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 failure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Borderline personality disorder			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Depression			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (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
Suicide attempt			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (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
Thinking abnormal			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Chest X-ray abnormal			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Chest injury			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Femoral neck fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Joint dislocation			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Meniscus lesion			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Road traffic accident			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Traumatic fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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	1 / 168 (0.60%)	1 / 168 (0.60%)	0 / 168 (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
Angina pectoris			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Atrial fibrillation			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
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 failure congestive			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	0 / 168 (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
Coronary artery disease			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Sick sinus syndrome			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Tachycardia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Nervous system disorders			
Carpal tunnel syndrome			

subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (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
Convulsion			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Hemiparesis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Sciatica			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Polycythaemia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Conjunctival haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Retinal detachment			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 disorders			
Abdominal pain			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Abdominal pain lower			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Anal fissure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Colonic polyp			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Haemorrhoids			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Ileus			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Nausea			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Cholecystitis acute			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 retention			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Arthralgia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Appendicitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Cholecystitis infective			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Chronic tonsillitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Clostridial infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Endocarditis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Herpes zoster			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Incision site infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Influenza			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 discitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Necrotising fasciitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Osteomyelitis			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 / 168 (0.00%)	0 / 168 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 streptococcal			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Postoperative wound infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Staphylococcal infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Streptococcal bacteraemia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Wound infection bacterial			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 168 (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
Yersinia infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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			
Decreased appetite			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Diabetes mellitus			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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
Obesity			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 168 (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 up to 5 Years: Apremilast 20 mg	Apremilast Exposure Up to 5 Years: Apremilast 20/30 mg BID	Apremilst Exposure up to 5 Years: Apremilast 30 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 245 (16.73%)	6 / 87 (6.90%)	49 / 245 (20.00%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	2 / 245 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			

subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Metastases to lymph nodes			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Morton's neuroma			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Neuroendocrine tumour			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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			
Deep vein thrombosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			

subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Varicose vein			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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 prostatic hyperplasia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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

Ovarian cyst ruptured			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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 haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Bronchiectasis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Pulmonary embolism			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Psychiatric disorders			
Borderline personality disorder			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	3 / 245 (1.22%)	0 / 87 (0.00%)	0 / 245 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thinking abnormal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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
Investigations			
Chest X-ray abnormal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femoral neck fracture			

subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Joint dislocation			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Traumatic fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 245 (0.82%)	0 / 87 (0.00%)	0 / 245 (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 pectoris			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Coronary artery disease			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	2 / 245 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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
Myocardial infarction			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Tachycardia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Convulsion			

subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Sciatica			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Polycythaemia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Conjunctival haemorrhage			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Retinal detachment			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Anal fissure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Colonic polyp			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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
Haemorrhoids			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 245 (0.41%)	1 / 87 (1.15%)	0 / 245 (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
Inguinal hernia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	0 / 245 (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
Psoriasis			
subjects affected / exposed	5 / 245 (2.04%)	0 / 87 (0.00%)	0 / 245 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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 failure acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary retention			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
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 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
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			
Arthralgia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	2 / 245 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 245 (0.41%)	1 / 87 (1.15%)	0 / 245 (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
Foot deformity			
subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar spinal stenosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 245 (0.82%)	0 / 87 (0.00%)	3 / 245 (1.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	3 / 245 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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
Cholecystitis infective			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Chronic tonsillitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	0 / 245 (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
Diverticulitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Endocarditis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Gastroenteritis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Incision site infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Intervertebral discitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Necrotising fasciitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Osteomyelitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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	2 / 245 (0.82%)	0 / 87 (0.00%)	2 / 245 (0.82%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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 streptococcal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Staphylococcal infection			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Streptococcal bacteraemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 87 (0.00%)	0 / 245 (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
Wound infection bacterial			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	0 / 245 (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
Yersinia infection			

subjects affected / exposed	0 / 245 (0.00%)	1 / 87 (1.15%)	0 / 245 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 245 (0.00%)	0 / 87 (0.00%)	1 / 245 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Week 0-24: Placebo (Placebo-Controlled Phase)	Week 0-24: Apremilast 20 mg (Placebo- Controlled Phase)	Week 0-24: Apremilast 30 mg (Placebo- Controlled Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 168 (25.60%)	69 / 168 (41.07%)	80 / 168 (47.62%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 168 (1.19%)	6 / 168 (3.57%)	2 / 168 (1.19%)
occurrences (all)	2	6	2
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 168 (4.76%)	17 / 168 (10.12%)	18 / 168 (10.71%)
occurrences (all)	10	25	21
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 168 (2.38%)	1 / 168 (0.60%)	8 / 168 (4.76%)
occurrences (all)	5	1	9

Abdominal pain upper			
subjects affected / exposed	2 / 168 (1.19%)	3 / 168 (1.79%)	7 / 168 (4.17%)
occurrences (all)	2	3	10
Diarrhoea			
subjects affected / exposed	4 / 168 (2.38%)	20 / 168 (11.90%)	32 / 168 (19.05%)
occurrences (all)	6	20	37
Dyspepsia			
subjects affected / exposed	4 / 168 (2.38%)	4 / 168 (2.38%)	6 / 168 (3.57%)
occurrences (all)	4	4	6
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	5 / 168 (2.98%)
occurrences (all)	1	1	6
Nausea			
subjects affected / exposed	11 / 168 (6.55%)	16 / 168 (9.52%)	32 / 168 (19.05%)
occurrences (all)	12	18	41
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 168 (0.60%)	2 / 168 (1.19%)	0 / 168 (0.00%)
occurrences (all)	1	2	0
Depression			
subjects affected / exposed	1 / 168 (0.60%)	4 / 168 (2.38%)	1 / 168 (0.60%)
occurrences (all)	1	4	1
Insomnia			
subjects affected / exposed	3 / 168 (1.79%)	2 / 168 (1.19%)	3 / 168 (1.79%)
occurrences (all)	3	2	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	1 / 168 (0.60%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	2 / 168 (1.19%)	2 / 168 (1.19%)	1 / 168 (0.60%)
occurrences (all)	2	2	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 168 (1.19%)	2 / 168 (1.19%)	0 / 168 (0.00%)
occurrences (all)	2	3	0

Gastroenteritis			
subjects affected / exposed	0 / 168 (0.00%)	3 / 168 (1.79%)	3 / 168 (1.79%)
occurrences (all)	0	3	3
Nasopharyngitis			
subjects affected / exposed	5 / 168 (2.98%)	7 / 168 (4.17%)	8 / 168 (4.76%)
occurrences (all)	5	8	10
Sinusitis			
subjects affected / exposed	4 / 168 (2.38%)	4 / 168 (2.38%)	4 / 168 (2.38%)
occurrences (all)	5	4	4
Upper respiratory tract infection			
subjects affected / exposed	6 / 168 (3.57%)	10 / 168 (5.95%)	7 / 168 (4.17%)
occurrences (all)	8	10	8
Urinary tract infection			
subjects affected / exposed	3 / 168 (1.79%)	3 / 168 (1.79%)	2 / 168 (1.19%)
occurrences (all)	5	3	2

Non-serious adverse events	Apremilast Exposure up to 5 Years: Apremilast 20 mg	Apremilast Exposure Up to 5 Years: Apremilast 20/30 mg BID	Apremilst Exposure up to 5 Years: Apremilast 30 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 245 (61.22%)	17 / 87 (19.54%)	169 / 245 (68.98%)
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 245 (8.16%)	4 / 87 (4.60%)	26 / 245 (10.61%)
occurrences (all)	22	4	30
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 245 (12.65%)	2 / 87 (2.30%)	34 / 245 (13.88%)
occurrences (all)	54	2	54
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 245 (4.49%)	1 / 87 (1.15%)	13 / 245 (5.31%)
occurrences (all)	12	2	15
Abdominal pain upper			
subjects affected / exposed	5 / 245 (2.04%)	0 / 87 (0.00%)	15 / 245 (6.12%)
occurrences (all)	5	0	21
Diarrhoea			

subjects affected / exposed	33 / 245 (13.47%)	1 / 87 (1.15%)	51 / 245 (20.82%)
occurrences (all)	39	1	62
Dyspepsia			
subjects affected / exposed	8 / 245 (3.27%)	1 / 87 (1.15%)	14 / 245 (5.71%)
occurrences (all)	8	1	15
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 245 (4.08%)	1 / 87 (1.15%)	19 / 245 (7.76%)
occurrences (all)	14	1	23
Nausea			
subjects affected / exposed	30 / 245 (12.24%)	0 / 87 (0.00%)	41 / 245 (16.73%)
occurrences (all)	35	0	56
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 245 (2.86%)	0 / 87 (0.00%)	14 / 245 (5.71%)
occurrences (all)	7	0	19
Depression			
subjects affected / exposed	17 / 245 (6.94%)	1 / 87 (1.15%)	10 / 245 (4.08%)
occurrences (all)	21	1	11
Insomnia			
subjects affected / exposed	13 / 245 (5.31%)	0 / 87 (0.00%)	9 / 245 (3.67%)
occurrences (all)	13	0	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 245 (4.90%)	0 / 87 (0.00%)	15 / 245 (6.12%)
occurrences (all)	16	0	17
Back pain			
subjects affected / exposed	14 / 245 (5.71%)	0 / 87 (0.00%)	13 / 245 (5.31%)
occurrences (all)	15	0	14
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 245 (6.94%)	3 / 87 (3.45%)	19 / 245 (7.76%)
occurrences (all)	22	3	22
Gastroenteritis			
subjects affected / exposed	16 / 245 (6.53%)	0 / 87 (0.00%)	11 / 245 (4.49%)
occurrences (all)	18	0	11
Nasopharyngitis			

subjects affected / exposed	30 / 245 (12.24%)	3 / 87 (3.45%)	31 / 245 (12.65%)
occurrences (all)	58	3	58
Sinusitis			
subjects affected / exposed	21 / 245 (8.57%)	2 / 87 (2.30%)	21 / 245 (8.57%)
occurrences (all)	29	2	34
Upper respiratory tract infection			
subjects affected / exposed	41 / 245 (16.73%)	3 / 87 (3.45%)	36 / 245 (14.69%)
occurrences (all)	73	3	61
Urinary tract infection			
subjects affected / exposed	10 / 245 (4.08%)	3 / 87 (3.45%)	16 / 245 (6.53%)
occurrences (all)	22	3	26

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2010	1. Modification of contraception requirements: Use of non-latex condoms (except those made of natural [animal] membrane) permitted to facilitate inclusion of subjects with latex allergies. For clarification, specified that contraceptive sponges must contain spermicide. Use of a cervical cap deleted according to regulatory agency advice. 2. Addition/modification of questionnaires: EQ-5D added to assess subjects' health state. Licensed versions of the MOS Sleep Scale and the BASDAI replaced the versions found in publications. 3. Addition of Efficacy Results from Study CC-10004-PSA-001: The efficacy results from the Phase 2 study CC-10004-PSA-001 were added to support the rationale for the Phase 3 protocol. 4. Transfer of emergency contact information from the protocol to the Investigator Study Manual. 5. Clarification of handling of subjects who were assigned to PBO or apremilast during the EE at Week 16. 6. Revision of timing of transition of subjects to the final "optimal" dose of study medication from the time of regulatory approval to the time at which unblinded study data support this decision. 7. Addition of ACR 70 to study endpoints. 8. Focus of analysis of questionnaires on health-related quality of life, rather than pharmacoeconomics. 9. Clarification that subjects who participate in the PK/PD assessments must sign a separate informed consent for these assessments. 10. Clarification of handling of concomitant medications for PsA after Week 52 of the study.
02 August 2010	1. Updating of safety information from completed studies: Information from recently completed psoriasis and PsA studies, included in the apremilast Investigator Brochure Version 8 (dated 18 May 2010), were incorporated into this amendment. 2. Removal of restrictions on as-needed NSAIDs and narcotic analgesics: Use of these medications was allowed, except within 48 hours of a study visit. 3. Expansion of Table of Events to clarify the assessments to be performed at each visit. 4. Clarification of handling of serum lipid values above the ULN. 5. Allowance of up to 25 mg/week of parenteral MTX. 6. Allowance of up to 325 mg per day of aspirin (acetylsalicylic acid) for cardiovascular prophylaxis. 7. Clarification in Inclusion Criterion 6 that study subjects must be therapeutic DMARD failures.
28 January 2011	1. Modification of protocol language for clarification. 2. Amended the protocol to clarify the language around contraception methods to ensure that we precisely describe acceptable methods of contraception given the global nature of our trials. Added a statement into the protocol to ensure that appropriate education regarding contraception methods is provided by the investigator to the subject. 3. Modification to protocol deleting annual CXRs, allowing local treatment guidelines to dictate when CXRs are performed. 4. Alignment of exclusion criteria related to past malignancies across the entire apremilast Phase 3 program, giving investigators responsibility for determining subject eligibility for previously successfully treated local lesions. 5. Modification of Reasons for Discontinuation to align with what is displayed in the InForm database.

10 June 2011	1. Provide correction regarding the Celgene Therapeutic Area Head of the study. 2. Addition of weight determination at the Screening Visit. 3. Addition of a serum pregnancy test at baseline for FCBP. 4. A clarification in Section 6.2, Contraception Education, which directs the investigator to Section 7.2 of the protocol where the specific details regarding acceptable contraception for this study may be found. 5. A clarification in Section 6.6.4, Clinical Laboratory Evaluations, to indicate that a microscopic evaluation will be performed on all urine samples. 6. Modification to Inclusion Criterion Number 14 – The Female Birth Control inclusion criterion was updated to clearly define single or multiple forms of contraception that are acceptable for this study. 7. Addition of a footnote to Inclusion Criterion Number 14 – The Female Birth Control inclusion criterion, which clarifies that the female subject's chosen form of contraception must be fully effective by the time the female subject receives the first dose of study medication at randomization. 8. Modification to Inclusion Criterion Number 13 – Male Birth Control inclusion criterion, which clarifies that male subjects must use a "male" latex or nonlatex condom. 9. Descriptive text on how to record onset and end dates of SAEs on the SAE Report Form was deleted because it is no longer applicable.
20 April 2012	1. Updated the contact information for the Medical Monitor of the study. 2. Modification of Section 4.1 Study Design, Section 8.3 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 Section 9.2 Prohibited Concomitant Medications to allow the use of topical corticosteroids, retinoids or vitamin D analog preparations and/or phototherapy after the Week 52 study visit for worsening skin psoriasis. 5. Addition of a footnote to the Adverse Events row in Table of Events, Section 5, (Tables 1 and 2) which reminds investigators to perform vasculitis assessments and/or psychiatric evaluations as appropriate, when adverse events are reported. 6. 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 precautionary 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 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. Change to the open-label IP packaging is described in Sections 6.10.1 and 8.5. 11. Addition of a note to Section 7.2, Inclusion Criterion 14, to refer investigators to Section 6.2, Contraception Education. 12. The term "CRF" 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 made at 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 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 Psoriatic Arthritis Response Criteria (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 assessed at Week 16, in addition to Weeks 24 and 52. 8. Modification of Protocol 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